DOES-NOT-CIRCULATE

UNIVERSITY OF MICHIGAN
SEP 30 1953
MEDICAL LIBRARY

BRITISH MEDICAL JOURNAL

JOURNAL OF THE BRITISH MEDICAL ASSOCIATION

SATURDAY SEPTEMBER 12 1953

TABLE OF CONTENTS

Tuberculosis and Leprosy : Immunological Studies in Healthy Persons
JOHN LOWE, C.B.E., M.D., M.R.C.P., and F. MCNULTY 579

Bronchial Carcinoma : Incidence and Aetiology.—II RICHARD DOLL, M.D., M.R.C.P. 585

The Approach to Psoriasis JOHN T. INGRAM, M.D., F.R.C.P. 591

Urinary Steroid Excretion in Rheumatoid Arthritis
A. E. KELLIE, PH.D., and A. P. WADE, PH.D. 594

Post-gastrectomy Syndrome J. EWART SCHOFIELD, F.R.C.S., and P. ST.G. ANDERSON, F.R.C.S.Ed. 598

A Rabbit Serum Containing a Specific Agglutinin for the Red Cells of the Newborn
ELIZABETH W. IKIN, B.SC., H. LEHMANN, M.D., PH.D., F.R.I.C., and A. E. MOURANT, M.A., D.M., D.Phil. 602

Alcohol-induced Pain in Hodgkin's Disease JAN G. DE WINTER, M.D., D.M.R. 604

Fatal Anaphylactic Shock Due to Penicillin
FRANK J. PICK, M.D., and JAMES F. PATTERSON, M.B., Ch.B. 605

Local Infection with Pasteurella Septica Following a Dog-bite
D. F. V. BRUNSDON, M.B., B.S., and B. L. MALLETT, M.B., B.S. 607

MEDICAL MEMORANDUM

The Age of the Menarche in the Tropics. DAGMAR C. WILSON, M.D., M.R.C.P., F.R.C.O.G., D.P.H., and IAN SUTHERLAND, M.A., D.Phil. 607

BOOK REVIEWS 608

GENERAL ARTICLES AND NEWS

First World Conference on Medical Education 615
UNIVERSITIES AND COLLEGES 631
VITAL STATISTICS 631
MEDICAL NEWS 633

OBITUARY

W. N. Searle, M.B., F.R.C.S., F.R.C.O.G. .. 630
H. Ll. Rutter, M.B.E., M.D., F.R.C.S. 630
Philip Talbot, M.B., F.R.C.S. 630
K. E. Eckenstein, M.B. 630

LEADING ARTICLES

Retrolental Fibroplasia 610
Resins and Cardiac Oedema 611

ANNOTATIONS

Infant Deaths 612
Genes and Enzymes 613
Lead in Lollies 613
Sanitary Inspectors 614
Infective Hepatitis in Doctors 614

SUPPLEMENT

Full Contents on First Page of Supplement
The N.H.S. in 1952 97
Notes and News 98
Correspondence :
Monthly Payment. P. D. WARREN, M.R.C.S. 98
The Small-list Doctor. MARY HERFORD, M.B.; H. BARBARA WOODHOUSE, M.B. 98
Rural and Urban Mileage. R. STUART, M.R.C.S. 99

CORRESPONDENCE

Aetiology of Vascular Disease. J. B. OLDHAM, F.R.C.S., and H. S. PEMBERTON, F.R.C.P. 628
Breast-feeding. ELENORA J. SIMPSON, M.B. 628
Non-paralytic Poliomyelitis. A. P. GRIMBLY, M.B. 628
Use and Effectiveness of Antimalarial Drugs. J. J. MESSENT, M.R.C.S. 629
Danger of Penicillin Injection. E. J. MASTERS, M.B. 629
Medical Education Conference. ST. GEORGE B. DELISLE GRAY, M.D. 629

QUESTIONS AND COMMENTS

Treatment of Subacute Combined Degeneration of the Cord—The Sexual Hair—Should an Epileptic ever Drive a Car ?—Cyclical Buccal Ulceration—Filatov's Tissue Therapy—Resuscitation After Coal-gas Poisoning—*N.F.* Lotions for Acne—Muscle Extracts—Correction 633-4

BRITISH MEDICAL ASSOCIATION, TAVISTOCK SQUARE, LONDON, W.C.1

No. 4836, WEEKLY, PRICE 3/-

Copyright

REGISTERED AS A NEWSPAPER

BAGS AND CASES

No. 1966

Size : 18 × 11 × 6 in. A hard-wearing case in dark brown cowhide. 3 drawers, space for sphygmomanometer. Rack with 3 bottles. Pocket in lid for papers. Price **£8 5s. 0d.**

No. 1954 The Portman

Size : 14½ × 10½ × 4½ in. An exceptionally light and useful case. Space for sphygmomanometer. Room for diagnostic, etc., instruments. Pocket in lid for papers.

Price **£5 7s. 6d.**

MIDWIFERY FORCEPS

STAINLESS STEEL
with and without
axis traction

JOHN BELL & CROYDEN

MAKERS OF SURGEONS' INSTRUMENTS AND HOSPITAL EQUIPMENT

WIGMORE STREET · LONDON, W.1

'Phone : WELbeck 5555 (20 lines). 'Grams : 'Instruments, Wesdo, London

★ Made from the finest Sheffield steel, Swann-Morton surgical blades are individually tested for keenness and flawlessness — then sterilised and coated with pure Vaseline to reach the surgeon's hands in perfect condition. Handles are of stainless metal, precisely machined to ensure that blades fit accurately and rigidly. There are eleven types of blade, as illustrated, and three types of handle.

Swann-Morton

W. R. SWANN & CO. LTD · PENN WORKS · SHEFFIELD · ENGLAND

VALOXYLIN

Trade Mark

Whole liver extract reinforced with vitamin B12

For the treatment of pernicious anaemia with or without neurological manifestations and for those other types of macrocytic anaemia which also respond to liver therapy. For sprue and as a general tonic.

Literature and prices on request.

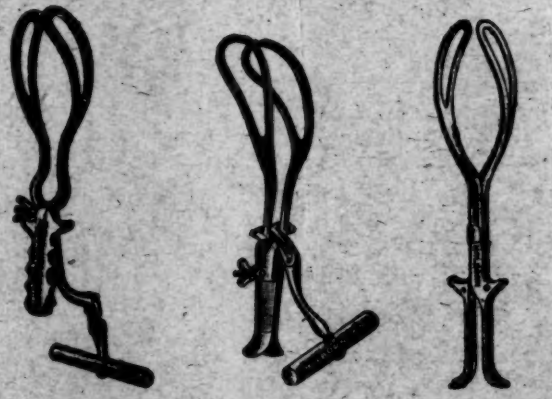
AN OXOID PRODUCT

OXOID

OXO LTD (Medical Dept.) Thames House, London, E.C.4 Tel. CENtral 9781

MIDWIFERY FORCEPS

FORGED FROM FINEST SHEFFIELD STAINLESS STEEL



GP 1472 GP 1473 GP 1469

GP 1472 Barnes' Midwifery Forceps with Simpson's handle and Neville's axis traction rod, stainless steel	£11 10 0
GP 1423 Ditto Anderson as above without axis traction, stainless steel	£8 0 0
GP 1473 Haig Fergusson's with axis traction, stainless steel ...	£11 10 0
GP 1471 (not illustrated) Ditto Milne Murray's	£13 10 0
GP 1469 Kielland's stainless steel	£8 10 0

Abridged catalogue on application

Inquiries invited for Obstetric Outfits and Instruments in general

HOLBORN SURGICAL INSTRUMENT Co. Ltd.
15 Charterhouse Street, Holborn Circus, London, E.C.1
Tel. : HOLborn 2268 (2 lines)

BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 12 1953

TUBERCULOSIS AND LEPROSY: IMMUNOLOGICAL STUDIES IN HEALTHY PERSONS

BY

JOHN LOWE, C.B.E., M.D., M.R.C.P.

Specialist, Nigeria Leprosy Service, Uzuakoli, Eastern Nigeria

AND

F. McNULTY

Laboratory Superintendent, Nigeria Leprosy Service, Uzuakoli, Eastern Nigeria

For more than 20 years some leprosy workers have entertained the idea that persons who, as the result of an abortive primary infection, are immune to tuberculosis may show some degree of immunity to leprosy. Certain clinical, epidemiological, and immunological findings pointed, rather vaguely it is true, to this conclusion. The advent of B.C.G. vaccination as a prophylactic measure in tuberculosis obviously added importance to this matter. Starting with the paper by Fernandez (1939a), several workers have reported that B.C.G. vaccination of healthy persons converts not only a negative response to tuberculin into a positive one, but also a negative response to lepromin into a positive one in the same person. Moreover, Fernandez (1943) reported that lepromin-negative healthy persons could be made lepromin-positive by the injection of suspensions of the tubercle bacillus or the leprosy bacillus killed by heat. Most leprosy workers consider that a positive lepromin test indicates a degree of immunity to leprosy. Some such workers have therefore been strongly advocating the use of B.C.G. vaccination in persons, particularly young children of leprous parents, who are intimately exposed to leprous infection, and good results from this measure are already being reported.

The matter is obviously one of great interest and importance; a simple and reliable method of immunizing "contacts" against leprosy might prove a very potent weapon in anti-leprosy work.

Further, some workers, among whom the chief is Chaussinand (1950), think that this cross-immunity between leprosy and tuberculosis is of profound epidemiological importance. This cross-immunity is believed to make leprosy and tuberculosis act as antagonistic diseases. A study of the history of leprosy and of tuberculosis in the world as a whole, and in individual countries, shows that leprosy is the earlier disease to spread, that tuberculosis appears later and spreads, and that leprosy then declines and finally disappears. This decline and disappearance of leprosy is thought by Chaussinand to be caused by the spread of tuberculous infection, making the population relatively immune to leprosy. Chaussinand quotes a large number of reports from different countries that the spread of tuberculosis is accompanied or followed by a decline in leprosy. He, and others, think that B.C.G. vaccination should in the future have the same effect in causing a decline in leprosy as he believes the spread of tuberculosis to have had in the past. He advocates the use of B.C.G. in the control of leprosy and of tuberculosis in countries where leprosy is still common "and the future extension of tuberculosis constitutes such a terrible menace." Such countries include most of Africa and much of Asia and South America.

These theories of Chaussinand seem so revolutionary as to provoke an immediate reaction of scepticism and adverse criticism. Careful consideration, however, is justified. The evidence Chaussinand quotes is, as he realizes, not conclusive, but it is strong. These theories, if confirmed, would throw a flood of light on the epidemiology of leprosy, which is very obscure, and would help to explain facts hitherto quite inexplicable—for example, the marked decline of leprosy in Europe between A.D. 1400 and 1800, the difficulty with which leprosy now spreads in European countries where it used to flourish, and so on.

This matter cannot be pursued here; it is mentioned to make it clear that we are discussing matters of great theoretical and practical interest and importance.

So far the work on this subject has been done almost entirely by South American and French workers; a British contribution to the subject is overdue. In the present article we attempt to review the available literature on the subject, to assess its value and significance, and at the same time to report on the early phases of a practical study of the subject, which aims at being as intensive and extensive as circumstances here in Nigeria permit.

The Lepromin Test

The lepromin test constitutes the results of attempts of many workers over many years to develop in leprosy a test similar in nature to the tuberculin test in tuberculosis.

In leprosy the bacilli cannot be cultivated, and experimental animals are not susceptible; therefore the only source of bacillary material is the lesions of patients suffering from the disease. In leprous nodules the bacilli are very numerous, counts as high as 1,000 million per

cubic centimetre of tissue having been recorded by Hanks (1945). By excising such nodules, sterilizing by heat, and by grinding them up in saline, vast numbers of bacilli are liberated, and suspensions of this nodular material can be made suitable for injection. Such suspensions contain in addition to bacilli tissue cells, fluids, and lipoids; but the antigenic material is the bacilli.

The lepromin test was originated by Mitsuda (1916, 1924), who in 1916 found that when a suspension of leprosy bacilli was injected intradermally a nodule developed in two to four weeks and then slowly subsided. In many healthy children the result was negative; with increasing age many healthy persons became positive, even in the absence of exposure to leprous infection; in the benign ("tuberculoid") forms of leprosy the test was almost invariably positive; in the malignant ("lepromatous") forms of leprosy the test was almost invariably negative. A positive test has long been accepted as indicating a degree of immunity to leprosy, the nature of that immunity, however, not being clear. The test is of very little value in diagnosis, but is useful in prognosis.

The nature of the reaction and the anomalous features of the reaction—(1) the lateness of the result, (2) the positive results in non-contact adults, and (3) the negative results in malignant (lepromatous) leprosy—have been the subjects of special studies.

Nature of the Positive Response to Lepromin

In brief, three different theories have been held by different workers. A few—for example, Bargehr (1926) and Rotberg (1937)—have regarded a positive test as being caused by specific allergy to the leprosy bacillus and its products of disintegration. This view appears no longer tenable and now seems to have few, if any, supporters. Rotberg himself has changed his mind on this matter.

Others have considered a positive reaction to be neither allergic nor specific, but think that a positive reaction is due to "resistance" of the body tissues to the bacilli, and that a negative reaction was due to lack of this "resistance." (The meaning of this term resistance was never clearly defined.) This position seems to have been undermined by more recent work, reviewed later.

Most workers have regarded the positive reaction as allergic, but not specific in nature.

The work of Fernandez and of Dharmendra has cleared up some anomalies. Fernandez (1939b, 1940) showed that a positive late response (two to five weeks) was almost always preceded by a "tuberculin-like" early response at 24–48 hours, consisting of a definite area of erythema and oedema surrounding the point of injection. Others—for example, Lowe and Dharmendra (1941)—soon confirmed this, and these workers also showed that, by grinding the bacilli for several hours till the bacillary forms were few or no longer found, and by suspending in saline and injecting the résidue, the early response was greatly increased and the late response was much diminished. They interpreted these findings as indicating that (*a*) both the early (Fernandez) and the late (Mitsuda) reaction to injection of lepromin were allergic in nature, and, moreover, (*b*) that they were both due to the same antigen, the early reaction being caused by free antigen present in the lepromin and the late reaction by slow liberation of the same antigen from the bacilli by slow disintegration at the site of injection. These findings were supported by histological studies. Fernandez, however, interpreted his findings as indicating two antigens, one active at 24 to 48 hours, and the other at two to five weeks.

Wade (1941, 1950) expressed still another view of the mechanism of the late reaction. He thought that in some persons—for example, non-contacts—the test might not reveal the presence of allergy at the time of the injection of lepromin, but only of potential allergy. In persons who were only potentially allergic, when lepromin was injected the allergy induced by the injection showed itself two to five weeks later by reaction at the site of injection, where bacilli were still present. Persons who were not even potentially allergic showed no such reaction.

Ideas rather similar to those of Wade in certain respects have been expressed by other workers, several, including Fernandez (1943), having considered that some inherent constitutional factor influenced the results of the lepromin test. For example, Rotberg (1937) thought that many people, probably the majority, were potentially allergic to the leprosy bacillus, and that when infected with leprosy they developed either no disease or else the mild "maculo-anaesthetic" form, these being the lepromin-positive persons; on the other hand, some, probably a minority, were inherently incapable of reacting allergically to lepromin or to leprous infection, and, if infected with leprosy, they developed the severe "nodular" or lepromatous form of the disease, the lepromin test remaining of course negative.

These ideas, if true, would have an important bearing on the question of the possibility of immunization against leprosy; in that connexion they are discussed below.

There still seems to be no unanimity of view among leprosy workers regarding the nature and mechanism of the reaction to lepromin. Fernandez, Lowe and Dharmendra, and Wade accept allergy as the basis of the reaction. We have seen no reason to abandon the view expressed by Lowe and Dharmendra that one antigen only operates, and Dharmendra's later work supports that view, for in 1942 he developed a method of completely separating leprosy bacilli from leprous tissue, and preparing lepromin which could be standardized by weight. Moreover, he (1941) was able to isolate various chemical fractions of such isolated bacilli; he isolated soluble antigenic fractions (protein) from the bacillus, which give a marked early reaction and no late reaction; and he failed to isolate any fraction which gave a late reaction only.

Regarding specificity, the positive findings in people never exposed to leprous infection have already been mentioned, and are discussed more fully later. Dharmendra and Jaikaria (1943) failed to find any fraction of the leprosy bacillus which when injected gave a response only in cases of leprosy and in contacts. They and others regarded infection with the tubercle bacillus as a possible or probable cause of non-specific response to the injection of lepromin. Recent work, more fully discussed below, supports this idea.

This, then, is the present position of the lepromin test. It is regarded as allergic, but non-specific or rather group-specific, and of value mainly in classification and prognosis. The injection of lepromin can produce two responses—an early (24 to 48 hours) response of tuberculin type (the Fernandez phenomenon) and a late (two to five weeks) response of nodular type (the Mitsuda phenomenon); both these responses have, in the opinion of some workers, the same significance, although some other workers think that the early response indicates "sensitivity" and the late response indicates immunity. The grounds for this differentiation are not clear, and it is not possible here to discuss this matter further.

Finally, it should be stated that in lepromin-positive persons the results of the test are usually very constant over many years. While there may be some variation in the degree of positivity, changes from positive to negative are rare.

The Tuberculin Test

There is almost universal agreement that a positive result is an allergic phenomenon which indicates sensitization to the tubercle bacillus and its products, introduced into the body in the form of a natural infection, or by the procedure of B.C.G. vaccination.

On the whole, the specificity of the tuberculin test remains without serious challenge. A positive result indicates tuberculous infection past or present. A negative result, however, does not necessarily indicate the absence of such infection. Even in severe tuberculous disease—for example, in miliary tuberculosis and in the last stages of pulmonary tuberculosis—the tuberculin test may be, or become, negative, indicating an anergy (which recalls in some respects the anergy of lepromatous leprosy).

This brings us to one point about the tuberculin test which should be mentioned. It is apparently not unusual for the results of the test to change from positive to negative and vice versa. It has been suggested that the test remains positive only in the presence of infection, which is often, however, latent and inactive. After complete eradication of tuberculous infection a positive tuberculin test may slowly become negative; with reinfection it may become positive again. Further, with progressive spread of the disease in the patient, a positive may become negative. Similar findings are recorded after B.C.G. vaccination. The positive tuberculin reaction induced by this measure is often short-lived, and to maintain positivity repeated vaccination is often necessary.

These findings contrast with the persistence of the response in the lepromin test.

Methods of Testing Used in the Present Study

The lepromin was prepared by a modification (necessitated by local conditions) of the method of Dharmendra (1942), and it was standardized biologically by comparison with a lepromin prepared by Dharmendra's (unmodified) method of preparing lepromin standardized by weight.

This lepromin has proved very satisfactory, and is maintaining its potency very well. The early (24 to 48 hours) response in our dark-skinned Africans is often not easy to read with accuracy; but a definite early response has always been followed by a marked late (two to five weeks) response. The late response has been one used here in recording the result as positive, doubtful, or negative.

In deciding what is positive, the following criteria have been adopted. A positive result means a definite nodule easily palpable and usually easily visible, detectable in the third and fourth weeks and often earlier and later. "Pinhead" nodules have been ignored in this work. The nodules recorded as positive have measured 4 to 10 mm. or more in diameter in the third and fourth weeks, the large ones often showing superficial alteration. In only a few cases have the results been recorded as doubtful.

The tuberculin used in this work was obtained from the Pasteur Institute, Paris. In all cases a preliminary scratch test (cuti-reaction) was done with crude tuberculin, undiluted, the readings being made at 48 and 72 hours; if a definite reaction was obtained no further test was done. Patients in whom results were doubtful and negative were then given an intradermal injection of 50 international units of purified tuberculin. In practice a definite raised area of erythema and oedema measuring 8 or more mm. in diameter was recorded as positive, though the nature of the reaction rather than the measurement was the deciding factor in a few doubtful cases. (In some doubtful cases a further test with 1 in 100 tuberculin was done, but these results are not recorded here.)

Findings of the Present Study

The following are the results of the lepromin and tuberculin tests in healthy Africans here in Uzuakoli.

Children Aged 1–15.—Of the 81 tested, 47 (58%) were tuberculin-positive and 31 (35%) lepromin-positive. From these data it is possible by simple calculation to find the proportion of cases in which the results of the two tests should agree or disagree, and in what way they should agree and disagree, if the two tests are entirely independent. The expected and actual figures are shown in Table I. It will be seen that the actual results obtained were very different from those expected if the two tests are entirely independent. Moreover, these differences when examined statistically (this has been done for us by Dr. B. Nicholson) are highly significant. The two tests are not independent; the results of the two tests agree far more often than they should do if they were independent.

TABLE I

	Both Tests Pos.	Both Tests Neg.	Tuberculin-pos. Lepromin-neg.	Tuberculin-neg. Lepromin-pos.	Disagreement
Expected	22%	26%	36%	16%	52%
Actual ..	(31) 38%	(34) 42%	(16) 20%	Nil	20%

Adults.—Of the 278 tested, 223 (80.2%) were tuberculin-positive and 224 (80.5%) lepromin-positive.

The results by the methods outlined above are shown in Table II. In this group of adults, with both tuberculin- and lepromin-positive rates much higher than those in children, the findings are less striking, and the differences between the results calculated on the basis of the two tests being independent and the actual results observed are less marked than in the children; nevertheless the differences are of the same nature, and, moreover, statistical analysis shows that they are significant, and that there is a greater agreement between the results of the two tests than can occur by chance.

TABLE II

	Both Tests Pos.	Both Tests Neg.	Tuberculin-pos Lepromin-neg.	Tuberculin-neg. Lepromin-pos.	Disagreement
Expected	64·6%	3·8%	15·6%	16·0%	31·6%
Actual ..	(201) 72·3%	(32) 11·5%	(22) 7·9%	(23) 8·3%	16·2%

Findings of Other Workers

We now look at the results of similar studies made by workers in other countries, and analyse them in the same way. Dharmendra and Jaikaria (1941) studied 260 healthy persons in the Punjab, where there was practically no leprosy and very little tuberculosis. The expected figure was 50.6%, and the actual 31.5%. In Indo-China Chaussinand (1949) tested 231 children of 4 to 8 years. Here the expected figure was 46.5% and the actual 18.6%. The same worker (Chaussinand, 1950) examined 38 children in Paris, and the figures were 49.8% expected and 2.6% actual.

All three studies—our present study, the previous studies of Dharmendra and Jaikaria, and those of Chaussinand—made in different countries by different workers at different times, the methods used also differing, point to the same conclusions, the two tests are not independent, and there is some factor operating strongly to make the two tests agree. What is this factor?

Cause of Agreement between the Two Tests

Four possibilities have to be considered.

1. Exposure to leprous infection (in Nigeria leprosy is highly endemic, and many if not most of the persons tested have had contact with leprosy cases) might have made persons allergic to both the leprosy and the tubercle bacilli. If this hypothesis were true, patients with leprosy of the allergic (tuberculoid) type should be tuberculin-positive. As is recorded elsewhere, this is often not so. There is practically no evidence to support this hypothesis; nearly all the evidence is against it.

2. It might be postulated that persons had been exposed either to both infections or else to neither, although it would not be easy to explain how this might occur, in Nigeria at any rate. But this argument is upset by the fact that in persons never exposed to leprous infection and living in

countries with no leprosy the two tests agree in a still higher proportion of cases. This is shown in the reports of Chaussinand (1950) and of Fernandez (1939a) on studies in Paris.

3. It might be postulated that some other factor, possibly some other acid-fast infection, is making people allergic to both the tubercle bacillus and the leprosy bacillus. This is perhaps less improbable than it might appear. Acid-fast bacilli are very common in nature, and can be found, isolated, and cultivated from many natural sources. Very few of them are known to be pathogenic to man, but that does not mean that they could not infect man, and perhaps produce in man the power to react allergically to themselves and to other acid-fast bacilli, including the tubercle bacillus and the leprosy bacillus. Nevertheless there is no direct evidence to support this hypothesis.

4. It seems that much the most likely explanation is that exposure to tuberculous infection is making people allergic to the leprosy bacillus. On this basis it is easy to explain how most healthy persons in most countries are allergic to both bacilli or to neither. In West Africa, however, and in other countries with much leprosy, it is more than possible that some persons have been exposed to leprous infection but not to tuberculous infection, and this would explain those cases which are lepromin-positive but tuberculin-negative. There remain unexplained, however, the cases that are tuberculin-positive but lepromin-negative. Analysis of the 38 such cases in our present two series shows that nearly all of them are weakly positive to tuberculin, which suggests that the degree of reaction to tuberculin influences the response to lepromin. Further examination of our records supports this view. In our 278 healthy adults studied, 71 showed a definite reaction in the scratch test (cuti-reaction), which indicates a high degree of sensitization to tuberculin, and all except one of these showed a positive lepromin reaction, nearly all strongly positive. (Incidentally, one may record that one of these was in a person who had just left, by air and for the first time, a country with no leprosy.)

The observations recorded above afford strong evidence that exposure to tuberculous infection, as shown by a positive tuberculin test, can, and usually does, cause the lepromin test to become positive; in fact, the observations can be reasonably explained only on this basis; no other hypothesis appears able to explain the facts. This hypothesis is strongly supported by published work other than that already quoted.

The following workers have reported a high incidence of positive lepromin tests in adults in countries where there is little or no leprosy, and where the possibility of the positive results being due to leprosy can be ignored. Cummins and Williams (1934) in England; Dubois (1936) in Belgium; Boncinelli (1937) in Italy; Fernandez (1939a) in Paris; Convit et al. (1944) in New York; Azulay and Convit (1947) in Ohio; Bechelli *et al.* (1945) in New York; Dharmendra and Jaikaria (1941) in the Punjab; and Chaussinand (1950) in Paris. Several of these workers have commented on the fact that tuberculin-positive persons studied were usually lepromin-positive.

Effect of B.C.G. Vaccination on Lepromin and Tuberculin Tests in Healthy Persons

The following published reports on this matter are available. Fernandez (1939a) reported that in persons negative to both tests B.C.G. vaccination usually made both tests positive. He studied 122 children with no contact with leprosy or tuberculosis, all being lepromin- and tuberculin-negative. After B.C.G. vaccination 99% became tuberculin-positive and 95% became lepromin-positive.

Neyra Ramirez (1951) took 53 healthy persons negative to both tests, and gave B.C.G.; 87% became lepromin-positive.

Chaussinand (1950) took 30 children negative to both tests, and found that all became lepromin-positive after B.C.G. vaccination.

Azulay (1948) gave B.C.G. to 15 lepromin- and tuberculin-negative children; 12 became tuberculin- and lepromin-positive.

Gines and Poletti (1946) studied 31 healthy children of leprous parents, giving B.C.G. vaccine: 25 were found lepromin-positive after vaccination. Of 11 in whom a previous lepromin test was not done, 9 were found positive; and of 20 in whom a previous test was negative, 16 became positive.

Rosemberg *et al.* (1950a) studied 39 healthy children of leprous parents, all tuberculin- and lepromin-negative. In 27 B.C.G. was given daily and orally for 28 days in increasing doses, with a total dosage of 1.19 g.* In all 27 the lepromin test became positive; the tuberculin test became positive in 24 and doubtful in 3. In the other 12 children only one dose of B.C.G. (0.1 g.) was given. Nine became tuberculin-positive and eight became lepromin-positive; three remained tuberculin- and lepromin-negative. Rosemberg *et al.* (1950b) studied 36 healthy tuberculin-negative children of healthy parents. B.C.G. was given orally for 28 days. This B.C.G. vaccine produced tuberculin conversions in 25. Ten months later 24 of the 25 had become tuberculin-negative; the lepromin test was still found positive in all the 36. Thus the lepromin test had become and remained positive after B.C.G. vaccination (*a*) in the one case becoming and remaining tuberculin-positive; (*b*) in the 24 becoming tuberculin-positive but later reverting to negative; and (*c*) in 11 who had never even become temporarily tuberculin-positive. Their findings therefore indicated that by B.C.G. vaccine given orally conversions from lepromin-negative to lepromin-positive were more common and also much more persistent than the tuberculin conversions produced by the same vaccination.

Other reports on the action of B.C.G. in converting a lepromin test from negative to positive include those of Budiansky (1949) and Dauden Valls *et al.* (1951).

Present Work

B.C.G. vaccine has been given by intradermal injection of 0.1 mg. in 65 healthy persons, all of whom were tuberculin-negative, and all but seven lepromin-negative before the B.C.G. was given. The tuberculin and lepromin tests were repeated two to three months later.

Very Young Babies (13).—B.C.G. was given soon after birth. No preliminary tuberculin and lepromin tests were done, and they were presumed negative. After B.C.G. nine became tuberculin- and lepromin-positive, and four became doubtful lepromin-positive.

Older Babies (8).—Before B.C.G. all were negative to both tests. After B.C.G. three became positive to both, and four became tuberculin-positive and lepromin-doubtful.

Older Children (29).—Before B.C.G. all were negative to both tests. After B.C.G. 20 became positive to both tests, six became tuberculin-positive and lepromin-doubtful, and three were tuberculin-positive and lepromin-negative.

*In Brazil, where this work was done, the routine method of giving B.C.G. in the field is by the oral route. The dose used is now 100 mg. in a single dose. This dose is large but is tolerated extremely well. Moreover, this method has one great advantage in field work—that no preliminary tuberculin-testing is necessary; persons who are strongly tuberculin-positive can take 100 mg. of B.C.G. orally with no upset whatever. The extra cost of the large dose of B.C.G. is more than neutralized by the saving in time, staff, and work caused by the elimination of the preliminary testing. For research purposes, and where statistics of the conversion rates are needed, this oral method of administration without preliminary testing is of course useless, except in children within a few weeks of birth, when it can safely be presumed that tuberculin and lepromin tests will be negative. For field work on a large scale, this method obviously has great advantages. A study of its use in the mass B.C.G. campaigns now in progress in several countries would appear well worth while. At present, lyophilized B.C.G. in this dosage is not available. In Brazil they make their own B.C.G. in this dosage in liquid form, and it has to be used within 25 days. There seems to be no reason why doses of 100 mg. should not be lyophilized to keep up to one year. If this could be done the wide use of B.C.G. might be greatly facilitated.

Adults (15).—Before B.C.G. all were tuberculin-negative and seven were lepromin-positive. After B.C.G. all were positive for both tests.

Conversions.—Of 65 previously tuberculin-negative, 64 became positive. Of 58 previously lepromin-negative, 40 became positive and 14 became doubtful. Of 54 becoming lepromin-positive or doubtful, all became tuberculin-positive. Of 64 becoming tuberculin-positive, seven were previously lepromin-positive, and, of the rest, 40 became lepromin-positive and 14 more became doubtful. Three cases becoming tuberculin-positive did *not* become lepromin-positive. The tuberculin conversions were thus more numerous and definite than the lepromin conversions. All the lepromin conversions also showed tuberculin conversions; the tuberculin conversions did not always show a lepromin conversion. These findings are in accord with the previously recorded findings of the two tests in healthy adults. While it is seen that tuberculin conversions are more numerous, there is evidence (Rosenberg *et al.*, 1950b) that the lepromin conversions are more permanent. It also seems highly probable that the doubtful lepromin tests recorded after B.C.G. are significant.

Does a Positive Lepromin Reaction Indicate Immunity to Leprosy?

The general feeling of experienced leprologists is that it does. A person who is found lepromin-positive, even after prolonged and intimate contact with leprosy, is practically always free from signs of leprosy, or the disease is in the mild self-limiting form. Most workers believe that it is the power to react allergically to leprosy bacillus, and the immunity which accompanies this phenomenon, which keep the person free from the disease, or if the disease is acquired, keep it in the mild form. It must be admitted that the proof of this idea is not complete. Moreover, it may be that a positive lepromin reaction produced as a response to *leprous* infection might indicate immunity to leprosy, but one produced as response to *tuberculous* infection or to *B.C.G.* might *not* be accompanied by and indicate the presence of immunity to leprosy. These matters are not easy to investigate, but more information is highly desirable.

The only available information bearing on this matter is contained in reports by Fernandez (1951) and by Montestruc and Blaché (1950).

Fernandez states: "For several years I have had under observation a group of children who were inoculated with B.C.G. after birth and who have continued to live with their leprous parents. As yet, none of them has developed the lepromatous form." This statement would appear to imply that some have developed non-lepromatous forms of leprosy.

Montestruc and Blaché record a family in Martinique in which a lepromatous mother bore children in 1938, 1940, and 1941, and all three children were vaccinated with B.C.G. at birth, and revaccinated at 1, 3, 5, and 9 years. All children have remained with the mother. In 1950 their ages were 12, 10, and 9, and they were healthy, and tuberculin- and lepromin-positive. They reported four other similar cases in children aged 12, 9, 7, and 5. All were given B.C.G. at birth and two were revaccinated at 1 year. All have stayed with the mother and all are healthy. Four other similar children in similar circumstances but not given B.C.G. have developed leprosy, at the ages of 11 months, 3, 5, and 7 years; three are lepromatous cases. Montestruc and Blaché realize that their numbers are small, but suggest that B.C.G. deserves a thorough trial in the prophylaxis of leprosy.

Can B.C.G. be Recommended in the Prophylaxis of Leprosy?

Several experienced workers have already given their answer in the affirmative. Their answer is based on the experience already outlined. B.C.G. vaccine is now being widely recommended and used in the prophylaxis of leprosy, especially by French and South American workers, and in coming years much more evidence regarding its value may be produced. Until now the evidence is meagre and much of it is indirect; arguments are based largely on experience of tuberculosis with the tuberculin test and B.C.G. But there are eminent tuberculosis workers who consider that the value of B.C.G. in the prophylaxis of tuberculosis is not proved, and a similar situation may be expected among leprosy workers.

Regarding B.C.G. and leprosy, one interesting and possibly vital question arises. We have already outlined the theory of certain experienced workers who postulate that there are a few persons who are inherently incapable of reacting allergically to the leprosy bacillus, and that these exposed to leprous infection become the progressive and infectious lepromatous cases. If this theory is true, and if the inability to react allergically to the leprosy bacillus is inherent and hereditary, then B.C.G. vaccination does not appear likely to overcome it. In other words it is possible that B.C.G. vaccine "immunizes" only those (the majority) who are already potentially allergic and potentially immune and do not need immunization, but fails to immunize those persons (the minority) who are inherently susceptible and most need immunization.

We have studied four babies whose parents are both known to us as lepromatous cases under our own observation. All four babies were lepromin- and tuberculin-negative. After B.C.G., all four became tuberculin-positive, three lepromin-positive, and one lepromin-doubtful. Other workers have reported to us personally similar findings. It appears that any hypothetical inherent inability to react to lepromin is not acquired by direct heredity.

If *all* children of leprous parents, *even if both parents are lepromatous cases,* can be rendered allergic to the leprosy bacillus by B.C.G., the case for the use of B.C.G. in prophylaxis will be considerably strengthened.

We have now reached the following position. A positive lepromin reaction is generally accepted as indicating some immunity to leprosy. A positive lepromin reaction is often produced by tuberculous infection, as shown by the tuberculin test, and it can also be induced by B.C.G. vaccination. There is no clear indication that there are any persons who cannot be made lepromin-positive by B.C.G. vaccination, repeated and given orally if necessary (this can be done without ill effects, even if the tuberculin test is positive).

So far the position seems fairly clear. But an important question arises. If tuberculosis immunizes against leprosy, might we not expect all cases of leprosy to be tuberculin-negative, indicating a lack of immunity conferred by previous tuberculous infection? The answer to this question is that while the mild self-limiting forms of leprosy showing immunity (positive lepromin test) might be expected to be tuberculin-positive, the severe progressive cases showing no immunity (negative lepromin test) might be expected to show a negative tuberculin test.

Is this expectation fulfilled? The answer is a very definite negative. Lepromin-negative lepromatous cases of leprosy show a tuberculin-positive rate approximately equal to that of the community from which they are drawn, and also as high as or higher than the tuberculoid leprosy cases in the same area. Moreover, they frequently show tuberculous infection, and not infrequently die from it. The lepromatous case thus seems to disobey all the rules.

These findings refuse to be fitted into the picture we have been outlining. There are possible explanations or partial explanations. These lepromatous cases may have acquired serious leprosy before they became infected with tuberculosis, and by then it was impossible for the immunity induced by tuberculosis to manifest itself. There is some evidence that tends to confirm this view; for example, in some countries it is recorded that lepromatous leprosy usually arises early in life, and that leprosy appearing later is more often mild; but in other countries this appears not to be so. It is doubtful if these ideas explain the anomalies.

It is impossible to discuss this matter fully here. A careful study of the lepromin test, the tuberculin test, and B.C.G. vaccination in actual cases of leprosy has been made, and will shortly be published. It may, however, be said that the findings in lepromatous cases are very different from, and hardly reconcilable with, those of studies of healthy persons by the same methods here recorded. Our understanding of sensitivity and immunity in leprosy and tuberculosis is far from complete, and, while cross-sensitivity is proved and cross-immunity seems to be more than possible, there are some facts which cannot be reconciled with these ideas.

To return, then, to our question, "Can B.C.G. be recommended in the prophylaxis of leprosy?" The evidence is incomplete and some of it appears to be contradictory. There still remains doubt in the minds of some workers whether a positive lepromin reaction (particularly if induced by B.C.G.) really indicates immunity. Until such doubts can be resolved or confirmed, what is the reasonable attitude to adopt towards the question of B.C.G. immunization of persons with a view to preventing leprosy?

It seems to us that its use even at the present time is justified, but that certain conditions should be fulfilled: (1) It must not be used indiscriminately, but generally it should be confined to those healthy persons, mainly children, who are unavoidably exposed to leprous infection. (2) In countries where mass B.C.G. vaccination against tuberculosis is being adopted, it may be difficult so to confine its use. In such countries an attempt should be made to utilize the mass B.C.G. campaign to give evidence of the value of B.C.G. in the prevention of leprosy. In some areas it may be possible for the B.C.G. campaign to be carried out by the leprosy staff, and to be designed specially to give evidence of its value in the control of leprosy. (3) All work with B.C.G. in countries with much leprosy should be planned, carried out, and recorded in such a way that it can, in the future, give reliable evidence on the value of B.C.G. vaccination in the prevention of leprosy. (4) It should be made quite clear to everyone concerned that B.C.G. vaccination of those exposed to infection does not remove the necessity for taking every possible step to prevent or minimize contact between open cases of leprosy and healthy persons, particularly children.

Summary

The hypothesis that between tuberculosis and leprosy there exists a cross-immunity which may have an important bearing on the immunology, spread, prophylaxis, and epidemiology of leprosy is examined.

The nature of the lepromin test is discussed; a report is presented of the analysis of the results of simultaneous lepromin and tuberculin tests in 359 healthy persons in East Nigeria. The degree of agreement between the results of the two tests is found to be significant; the reason for the high degree of agreement is considered to be that tuberculous infection, as shown by the tuberculin test, makes people sensitive to lepromin as shown in the lepromin test.

The reports of other similar studies of the same subject by other workers in other countries are discussed and analysed in the same way, and give similar results.

The findings are presented of the study of the effect of B.C.G. vaccination on the lepromin and tuberculin tests in healthy persons. In 65 persons previously tuberculin-negative, 64 were made tuberculin-positive. Of 58 of the same persons previously lepromin-negative, 40 were made lepromin-positive and 14 were recorded as "doubtful." Lepromin conversions were seen only in persons who showed tuberculin conversions.

The question whether a positive lepromin test indicates immunity to leprosy is discussed, and the available evidence is presented; no definite conclusions are drawn, but the findings are thought to be suggestive.

The advisability of using B.C.G. vaccination of healthy people in countries where leprosy is common is discussed. Its value is regarded as not proved, for the evidence is incomplete and some of it is contradictory. Nevertheless, the view of Chaussinand, "that B.C.G. vaccine deserves to be widely used in areas where leprosy is common and is difficult to control, and where the future extension of tuberculosis constitutes such a terrible menace," is endorsed, with the proviso that the work should be so planned and carried out that it affords evidence of the value of B.C.G. vaccination in the control of leprosy and of tuberculosis, and that the use of B.C.G. shall not be regarded as rendering unnecessary the isolation of open cases from other persons, particularly children.

Thanks are due to Dr. R. Chaussinand and the Pasteur Institute, Paris, for supplies of purified tuberculin and of lyophilized B.C.G.; to the staff and students of the Methodist College, Uzuakoli, and to the staff of the Leprosy Settlement, Uzuakoli, for volunteering to be the subjects of experimentation; to the Leprosy Adviser to the Nigeria Government (Dr. T. F. Davey); and to the Inspector-General of Medical Services, Nigeria (Dr. S. L. S. Manuwa), for permission to publish this paper.

ADDENDUM.—I have received from Dr. H. W. Wade, Editor of the *International Leprosy Journal*, further information about the results of B.C.G. vaccination in the prevention of leprosy in Brazil. Dr. Nelson de Souza Campos has sent to Dr. Wade a letter on this subject for publication the main facts of which are as follows:

B.C.G. has been given orally to some "contacts" of leprosy cases at the Central Leprosy Dispensary in São Paulo. Of nearly 1,700 such contacts given B.C.G., 10 (0.6%) developed leprous lesions, all tuberculoid (mild). Of over 3,300 similar contacts not given B.C.G. 179 (5.4%) developed leprous lesions—some lepromatous (severe), some indeterminate, and some tuberculoid. No details are yet available.

REFERENCES

Azulay, R. D. (1948). *Hospital, Rio de J.*, **34**, 853.
—— and Convit, J. (1947). *Int. J. Leprosy*, **15**, 264.
Bargehr, P. (1926). *Z. ImmunForsch.*, **47**, 529.
Bechelli, L. M., Keil, H., and Rotberg, A. (1945). *Rev. brasil. Leprol.*, **13**, 21.
Boncinelli, U. (1937). *C. ital. Derm. Sif.*, **23**, 425.
Budiansky, E. (1949). *Rev. brasil. Leprol.*, **17**, 27.
Chaussinand, R. (1949). *Rev. colon. méd. Chir.*, **21**, 170. (Abstracted in *Int. J. Leprosy*, 1950, **18**, 441.)
—— (1950). *La Lèpre*, p. 148. Expansion Scientifique Française, Paris. Also *Int. J. Leprosy*, 1948, **16**, 431.
Convit, J., Azulay, R. D., Bermudez, D., and Salgado, P. (1944). *Int. J. Leprosy*, **12**, 60.
Cummins, S. L., and Williams, E. M. (1934). *British Medical Journal*, **1**, 702.
Dauden Valls, F., Moray Comas, J., and Dauden Sala, C. (1951). *Acta dermo-sifiliogr., Madr.*, **42**, 505.
Dharmendra (1941). *Leprosy in India*, **13**, 89.
—— (1942). Ibid., **14**, 122.
—— and Jaikaria, S. S. (1941). Ibid., **13**, 40.
—— —— (1943). Ibid., **15**, 40.
Dubois, A. (1936). *Bull. Soc. Path. exot.*, **29**, 649.
Fernandez, J. M. M. (1939a). *Rev. argent. Dermatosif.*, **23**, 425.
—— (1939b). *Ann. paulist. Med. Cirurg.*, **37**, 308.
—— (1940). *Int. J. Leprosy*, **8**, 1.
—— (1943). Ibid., **11**, 15.
—— (1951). Ibid., **19**, 474.
Gines, A. R., and Poletti, J. G. (1946). *Bol. Ofic. sanit. pan-amer.*, **25**, 884.
Hanks, J. H. (1945). *Int. J. Leprosy*, **13**, 25.
Lowe, J., and Dharmendra (1941). *Leprosy in India*, **13**, 81.
Mitsuda, K. (1916). Quoted by F. Hayashi, *Int. J. Leprosy*, 1933, **1**, 31.
—— (1924). *Proc. 3rd. Int. Leprosy Conf., Strasbourg.*, p. 219. Baillière, Paris.
Montestruc, E., and Blaché, R. (1950). *Rev. colon. méd. Chir.*, **15**, 358.
Neyra Ramirez, J. (1951). *Rev. Sanid. Policia*, **11**, 519.
Rosemberg, J., Campos, N. de S., and Aun, J. N. (1950a). *Rev. brasil. Leprol.*, **18**, 3.
—— —— —— (1950b). Ibid., **18**, 128.
Rotberg, A. (1937). Ibid., **5**, Spec. No. 45.
Wade, H. W. (1941). *Int. J. Leprosy*, **9**, 39.
—— (1950). Ibid., **18**, 487.

BRONCHIAL CARCINOMA: INCIDENCE AND AETIOLOGY*

BY

RICHARD DOLL, M.D., M.R.C.P.

Member of the Statistical Unit of the Medical Research Council

Consumption of Tobacco

The possibility that a relationship exists between the smoking of tobacco and the development of bronchial carcinoma has been suggested often—and over a period of many years. At first the suggestion was made either on theoretical grounds or because of the clinical observation that the patients tended to be heavy smokers. In support it was pointed out that national figures for tobacco consumption showed increases over the same period in which the recorded lung cancer death rates had increased. In the absence of positive animal experiments, or of detailed knowledge of normal smoking habits, such considerations carried little weight, and it is invidious to try to determine who first suggested that tobacco might be a factor.

Direct evidence of a relationship was first secured in 1939 by Müller, in Germany. He obtained the smoking histories of 86 male patients with bronchial carcinoma from hospital notes, by personal interview, or from a questionary sent to the relatives of the patients who had died; he compared them with histories given by 86 healthy men of the same ages. The results showed gross differences between the groups in the proportions of non-smokers and of heavy smokers, but the different methods by which the data were collected made it difficult to draw firm conclusions from the comparison.

Subsequently other workers have used similar methods to study the problem—that is to say, they have obtained records of the smoking habits of patients with bronchial carcinoma and have compared these with records of other subjects, assumed to be representative of the population from which the bronchial carcinoma patients were drawn. The principal results obtained in the reports to which I have been able to refer are shown in Table III.

TABLE III.—*Smoking Habits of Men With and Without Lung Cancer*

Author	Date	No. of Men		Percentage of Non-smokers* Among Men		Percentage of Heavy Smokers* Among Men	
		With Lung Cancer	Without Lung Cancer	With Lung Cancer	Without Lung Cancer	With Lung Cancer	Without Lung Cancer
Müller ..	1939	86	86	3·5	16·3	65·1	36·0
Schairer and Schöniger..	1943	93	270	3·2	15·9	51·6	26·7
Wassink ..	1948	134	100	4·8	19·0	82·0	45·0
Schrek *et al.*..	1950	82	522	14·6	23·9	18·3*a*	9·2*a*
Mills and Porter ..	1950	444*b*	430	7*b*	31	—	—
Levin *et al.* ..	1950	236	481	15·3	21·7	—	—
Wynder and Graham ..	1950	605*c*	780	1·3*c*	14·6	51·2*c*	19·1
McConnell *et al.* ..	1952	93	186	5·4	6·5	35·0*d*	21·5*d*
Doll and Hill	1952	1,357	1,357	0·5	4·5	25·0	13·4

* Definition varies from one author to another.
a. Percentage of heavy cigarette smokers.
b. Figures relate to all respiratory cancers.
c. Figures relate to lung cancer other than adenocarcinoma.
d Percentage among men and women (93 men and 7 women and 186 men and 14 women respectively).

The proportions of "non-smokers" and of "heavy smokers" found among both groups of men—those with and those without lung cancer—vary considerably from one author to another. This is not surprising, since the observations were made in four different countries, the definitions of "non-smoker" and "heavy smoker" varied considerably, and so did the methods by which the records were obtained. The notable fact is the consistency with which the proportions of non-smokers were lower and the proportions of heavy smokers were higher among the male patients with lung cancer than among the other men investigated.

In only one report is the difference in doubt. According to McConnell, Gordon, and Jones (1952) the proportion of non-smokers among 93 male patients with lung carcinoma in the Liverpool area was only slightly less than that among 186 male patients of similar ages but with other diseases. It is, however, possible that the definition of a non-smoker may not have been applied with equal rigour in both groups, since most of the lung cancer patients were interviewed two years before the controls and before the form of the investigation had been finally determined. In contrast, the proportion of "heavy" smokers was found to be significantly higher in the cancer group than in the control group—as in all other reports.

The consistency of the results of investigations carried out with various techniques in four different countries is, in itself, suggestive that a real relationship between smoking and lung cancer exists. The possibility that all the results could be due to bias in the selection or interviewing of patients has been eliminated, and there are strong reasons for believing that the control patients—in at least some of the investigations—were adequately representative of the populations from which the lung-cancer patients were drawn (Doll and Hill, 1950, 1952). The results amount, I believe, to proof that smoking is a cause of bronchial carcinoma. No proof is, however, absolute—all are susceptible to greater or smaller degrees of confidence. It is only by further experiment, by testing the hypothesis under fresh conditions, that confidence can be gradually increased until finally its truth is unquestioned.

In the present case, the simplest way of checking the conclusion is by observation of the mortality from bronchial carcinoma in subjects whose smoking habits have been previously defined. Such a check is being carried out by Hammond in the U.S.A., by Kreyberg in Norway, and by Bradford Hill and Doll in this country. In the British investigation, questionaries were sent to 59,600 doctors asking them to classify themselves into three groups, according to whether they continued to smoke, had given up smoking, or had never smoked regularly. If they fell into either of the first two categories they were asked additional questions—namely, the age at which they started to smoke, the amount smoked, and whether they smoked pipes or cigarettes. The questions were made short and few, to ensure the maximum number of replies and because the experience of interviews with nearly 5,000 patients in the earlier inquiry had shown that classification of smokers according to the present amount smoked and the number of years given up gave almost as sharp a differentiation between the bronchial carcinoma and other patients as the use of more complex statistics.

Altogether 40,603 replies have been received. The fact that this is only 68% of the number of questionaries sent out is immaterial, since we are not concerned to estimate the smoking habits of doctors as a profession for comparison with those of other professions, but to define groups within the profession who differ in the amount they smoke.

By the courtesy of the Registrars-General of Great Britain and Northern Ireland, it has been possible to receive details of the causes of death of all doctors who have died since the questionaries were sent out. In the first eleven months, nine deaths have been recorded due to lung cancer, among doctors aged 55 and over for whom details of the previous smoking histories are available. From the knowledge of the smoking histories of all the doctors who replied, mortality rates can be calculated for different levels of tobacco consumption—making allowance for the variation of smoking habits with age. Whilst the deaths are so few,

*Second part of the Milroy Lectures delivered at the Royal College of Physicians of London on February 10 and 12, 1953. (*Abridged.*) The first part was printed in last week's *Journal* (p. 521).

the calculated mortality rates are extremely unreliable, but so far as they go they are not inconsistent with the results recorded previously.

All forms of smoking are, it appears, not equally dangerous. Pipe-smoking (Wynder and Graham, 1950; Levin *et al.*, 1950; Schrek *et al.*, 1950; Doll and Hill, 1952) has, with one exception (McConnell *et al.*, 1952), been found to be less closely associated with bronchial carcinoma than has cigarette-smoking. This can be partly accounted for by the lower average consumption of tobacco by pipe-smokers; on the other hand, Doll and Hill have estimated that the risk is lower among pure pipe-smokers than among pure cigarette-smokers at each level of tobacco consumption. According to the American authors, cigar-smoking provides the same order of risk as pipe-smoking (Table IV).

TABLE IV.—*Relative Proportions of Cigarette-, Cigar-, and Pipe-smokers; Lung Cancer and Other Patients (American Authors)*

Authority	Ratio of Cigarette- to Pipe-smokers		Ratio of Cigarette- to Cigar-smokers	
	Lung-cancer Patients	Other Patients	Lung-cancer Patients	Other Patients
Wynder and Graham (1950)	22·8:1	5·3:1	26·1:1	8·4:1
Schrek *et al.* (1950) ..	16·4:1	5·1:1	21·7:1	5·9:1
Levin *et al.* (1950)	5·0:1	1·7:1	5·9:1	1·9:1

Users of cigarette-holders and smokers of filter-tipped cigarettes have been found less frequently among lung carcinoma patients than among patients with other diseases. The proportion of persons who have been accustomed to smoke in this way is small and the number of recorded observations is too few for firm conclusions; they are, however, consistent with the observations on pipe-smokers, and it seems probable that each of these methods of smoking may partly separate out an active agent before it reaches the respiratory tract (Doll and Hill, 1952).

In discussing the conclusions to be drawn from their preliminary data, Doll and Hill (1950) pointed out that to say that a real association existed between carcinoma of the lung and smoking was not the same as saying that smoking caused carcinoma of the lung. "The association would occur if carcinoma of the lung caused people to smoke or if both attributes were end-effects of a common cause. The habit of smoking was, however, invariably formed before the onset of the disease (as revealed by the production of symptoms), so that the disease cannot be held to have caused the habit; nor can we ourselves envisage any common cause likely to lead both to the development of the habit and to the development of the disease 20 to 50 years later. We therefore conclude that smoking is a factor, and an important factor, in the production of carcinoma of the lung."

In the two and a half years that have since passed there has been no reason to think that that conclusion needs to be modified. It has been challenged on a number of grounds, but only one appears to require serious consideration. The fact that no carcinogen has been identified in tobacco smoke does not invalidate the evidence; the recognition of the risk run by chimney-sweeps and tar-workers came many years before the carcinogenic polycyclic hydrocarbons were isolated. Nor is it significant that the increase in the recorded death rate has been greater than the increase in tobacco consumption, since we have so little idea what proportion of the recorded increase in mortality is real. The more serious objection is that it is theoretically possible for both smoking and the development of bronchial carcinoma to be themselves related to some third common factor. In view of the apparently linear increase in the mortality from lung cancer with increasing tobacco consumption, we should need to postulate that this third factor was also linearly related both to smoking and to the risk of developing the disease. In the absence of positive evidence that such a factor exists it is more reasonable to adopt the philosophical principle of Occam's razor, which has served science so well in the past, and to proceed on the basis of the simplest explanation; that is, that the more people smoke the more likely they are to develop carcinoma of the lung.

It has often been suggested that it is not so much the tobacco which is responsible for the carcinogenic action of the smoke as the cigarette paper or the associated use of a petrol lighter. Such a position cannot, I think, be maintained. In the first place, there would appear to be some risk associated with pipe-smoking (even though it may be appreciably smaller than that associated with cigarettes) and tar from tobacco burnt as in pipe-smoking has been shown to have a carcinogenic effect experimentally (Sanders *et al.*, 1932; Flory, 1941). Secondly, petrol lighters have not been used any more extensively by patients with bronchial carcinoma than by other patients.

Arsenic is present in most forms of tobacco, probably through its use as an insecticide. It is present in greatest amounts in tobacco of American origin and is completely, or almost completely, absent from Oriental types. Daff and Kennaway (1950) estimate that an ordinary "Virginian" cigarette, as smoked in England, contains about 50 μg., expressed as As_2O_3, and that approximately 15% is volatilized in smoking. Smoking 10 cigarettes a day means, therefore, that as much arsenic as is present in one maximum official dose of Fowler's solution is volatilized in 10 weeks. This is not a large amount, and in any case arsenic is unlikely to be the carcinogenic agent, since (1) a high proportion of cancer cases in Istanbul are found at necropsy to arise from the bronchi (Schwartz, reported by Daff, Doll, and Kennaway, 1951) and Turkish tobacco contains no, or very little, arsenic; and (2) tar from tobacco smoke, applied externally to the skin of animals, is capable of inducing cancer, which arsenic is not.

The last observation also tells to some extent against the suggestion that the agent in tobacco might be a co-carcinogen, which acted by enhancing the effect of another substance present in, say, the atmosphere of towns.

Benzpyrene has not been detected in tobacco smoke, and it would seem probable that the substance concerned is one which has not hitherto been recognized to be carcinogenic.

Other Aetiological Factors

Of other factors suggested as being of possible aetiological importance, the greatest attention has been paid to previous respiratory disease and hereditary predisposition.

Shaw suggested, in 1924, that patients who recovered from influenzal pneumonia might have an increased susceptibility to lung cancer, and he added, in relation to the pandemic of 1918–19, that it would be "of interest to see whether, as a late manifestation, there is an increase in the number of cases of pulmonary cancer, which at present is a relatively rare tumour." His surmise was based on observation of metaplastic changes in the bronchial mucosa of patients dying of subacute influenzal pneumonia; it has certainly been borne out in regard to the increased incidence of the disease, but the reason for the increase which he suggested seems unlikely to be correct. Firstly, there has been little increase of lung cancer in Iceland (Dungal, 1950), although that country suffered severely from the pandemic of influenza; and, secondly, influenza affected both sexes almost equally in Britain in 1918–19 (as judged by mortality), while deaths from lung cancer occur predominantly in men.

Schwartz (1950) has described cases of bronchial carcinoma arising in association with lesions of the bronchial wall brought about by neighbouring tuberculous lymph nodes. Woodruff and Nahas (1951), and Woodruff *et al.* (1952) have found that large calcified foci—larger than in any other part of the lung—were present in the same lobe as the tumour, or in the tracheo-bronchial nodes draining the lobe, in two-thirds of 40 cases of squamous and anaplastic bronchial tumours, while they found a similar focus in only

one of six bronchial adenocarcinomas. Woodruff suggests that calcified foci may increase the susceptibility of the neighbouring bronchial mucosa to carcinogenic substances reaching it from the inspired air or that bronchiectasis following primary tuberculosis may be a predisposing factor. On these assumptions, he suggests that part of the recent increase in bronchial carcinoma may be explained by the *fall* in mortality from pulmonary tuberculosis in young adult males, leading to the occurrence of an *increase* in the incidence of healed primary foci in older men a generation later. Whether such a corollary has in fact occurred is open to doubt and cannot be assumed in the absence of direct evidence. It is at least as likely that the decreased mortality in young males should have been followed by a decreased incidence of healed primary foci.

Through the courtesy of Dr. Norman Smith, of the Ministry of Health, I am able to refer to the statistics of mass radiography; these show that the incidence of healed primary tuberculosis, striking enough to be reported in miniature films, is practically constant above the age of 35 —that is, the incidence was 1.0% for men aged 35–44 and 1.1% for men aged 45–54 and for men over 60.

Bronchiectasis and chronic bronchitis have also been thought to predispose to the disease. No such action can, however, be deduced from the observation that a number of patients with bronchial carcinoma have suffered from these diseases. Neither disease is rare, and their incidence in bronchial carcinoma patients needs to be compared with some standard rate before any conclusion is justified. Doll and Hill (1952) have attempted to do this, and they concluded that either chronic bronchitis and pneumonia predispose to a whole group of respiratory disorders, including bronchial carcinoma, or else—and this seems more likely—that patients with respiratory disorders recall previous chronic bronchitis and pneumonia more readily than do patients with diseases in other systems. Whether previous respiratory disease plays any part in the aetiology of bronchial carcinoma is certainly not proved.

From analogy with pulmonary tumours in animals and with some types of cancer in man, it might be expected that hereditary predisposition would be of some importance in the development of carcinoma of the lung. Differences in incidence in different parts of the world may be partly attributable to racial differences in susceptibility, but the contrast between the experience of native Africans in Africa and of negroes in the U.S.A. suggests that large differences can readily be accounted for by the environment. The recent increase in incidence of the disease and the clear effect of occupation in certain industries demonstrate the importance of environmental factors; they do not, however, exclude the possibility that predisposition may also be variable. The presumption must be that it is, but that under optimum conditions it would seldom be strong enough to result in clinical disease.

Conclusion

It is now becoming possible to piece together the various independent observations and to begin to get a picture of the aetiology of the disease as a whole. Industrial hazards of great variety are responsible for a proportion of cases, but, with the exception of the production of gas, the industries with a recognized risk employ few workers and the total number of cases resulting each year is small. Although the incidence of industrial cases varies from one country to another, and falls most heavily on townsmen and almost exclusively on men, it does not contribute any significant part to the difference in incidence between countries, nor —except very locally—to the differences between urban and rural areas and between men and women. The importance of the observations is twofold. Firstly, they indicate the sources of risks which it is none the less essential to eliminate although only few men are exposed to them; and, secondly, they provide evidence of the nature of substances which can cause bronchial carcinoma and which may therefore, when derived from other sources, contribute to the production of the common non-industrial cases. Such substances appear to be radon and benzpyrene, products associated with the refining of nickel and the manufacture of chromates and asbestos, and probably arsenic.

Two other sources for the production of the disease have been recognized—namely, residence in towns and the smoking of tobacco. The carcinogenic factors concerned are, however, not necessarily distinct. There are, for example, fewer non-smokers, more cigarette-smokers, and more heavy smokers among Londoners than among the inhabitants of other towns and of rural districts, so that the effect of the tobacco factor alone will result in the incidence of bronchial carcinoma being higher in the big cities. On the other hand, from the death rates which have been calculated for persons smoking different average amounts over a ten-year period, the differences in smoking habits seem to be insufficient to account for the observed differences in mortality. These rates may not, however, be the appropriate ones to apply. The amount consumed over earlier periods must also be of some—and possibly of major —significance, and differences in cigarette consumption between areas may have been greater 20 or 30 years ago than they are now. In the present state of knowledge such possible differences cannot be allowed for and the most effective test of the independent action of the "urban factor" is the comparison of the mortality rates between different parts of the country in persons who do not now smoke and who have never done so in the past.

The material collected by Doll and Hill has already been used to calculate the mortality rates among non-smokers of different ages in Greater London. It is less suitable for estimating the mortality rates in other areas, since it was drawn from a few places only and may well not have been representative of the rest of the country. Nevertheless, it is of interest to see what indications may be obtained from it. The material has therefore been divided into three parts according to the patient's place of residence, and mortality rates have been calculated for non-smokers in towns other than London and in rural districts, in the same way as rates were previously calculated for Greater London (Doll, 1953). As a check, the rates have been recalculated, using the figures obtained by the Government Social Survey for the estimation of the total numbers of non-smokers at risk. The results are shown in Table V.

The greatest numbers of patients with bronchial carcinoma were interviewed in the age group 45–64, and this age group therefore provides the most reliable data. The similarity of the results obtained for each of the three areas is striking; it suggests that, in the absence of smoking, the "urban factor" is of little relevance. This may mean either that the "urban factor" is nothing but a reflection of the tendency for cigarette consumption per person to be greater in the larger towns or that it acts principally by increasing the effect of the tobacco factor. If this is so it may be easier to understand why the male mortality in Greater London should be only 2.1 times the mortality in English and Welsh rural districts, while the ratio of the rates between Norwegian towns and rural districts should be 2.5 to 1 and that between Copenhagen and Danish rural districts 4.3 to 1. It is unlikely that the air of Copenhagen and

TABLE V.—*Mortality from Lung Cancer among Non-smokers in Different Types of Area*

Age	Estimated Annual Death Rate per 1,000 Non-smokers			Source of Data for Estimate of Proportion of Non-smokers in Population
	Greater London	Other Towns	Rural Districts	
25– ..	0·005	0·026	(Less than 0·017)	Doll and Hill (1952)
45– ..	0·09	0·09	0·08	
65–74 ..	0·31	0·16	0·31	
25– ..	0·006	0·030	(Less than 0·017)	Government Social Survey
45– ..	0·09	0·09	0·07	
65–74 ..	0·28	0·16	0·37	

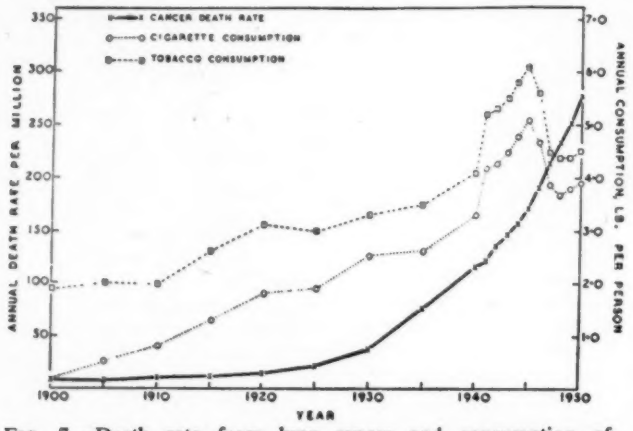


FIG. 7.—Death rate from lung cancer and consumption of cigarettes and of all tobacco, England and Wales, 1900–50. Cigarette and tobacco consumption estimated for Great Britain and Ireland prior to 1922, for Great Britain and Northern Ireland subsequently (Board of Trade Statistics).

Oslo should be relatively more polluted than the air of London. It may be, on the other hand, that the habit of cigarette smoking has spread less rapidly and less completely over the rural districts of Denmark and of Norway than it has over the countryside of Britain.

The other outstanding epidemiological observations relating to bronchial carcinoma are the dramatic increase in the recorded mortality over the last 25 years, the differences in incidence between different countries, and the predilection of the disease for men. Fig. 7 shows the recorded mortality in England and Wales and the consumption of cigarettes and of all tobacco products in Britain from 1900 to 1950. The increase in the annual consumption of tobacco has been moderate—from 1.9 lb. (0.86 kg.) to a maximum of 6.1 lb. (2.77 kg.) per person in 1945—but a marked change has taken place in the manner in which tobacco is used and a much larger increase has taken place in the annual consumption of cigarettes—from approximately 0.2 to 3.9 lb. (0.09 to 1.77 kg.) per person with a maximum, in 1945, of 5.1 lb. In other countries, changes in the pattern of tobacco consumption have taken place more recently and have been even more marked; in the U.S.A., for example, chewing-tobacco and cigars accounted for large fractions of the tobacco consumed until 1930. In the present state of knowledge, it is not possible, in my opinion, to relate such changes directly to the changes in mortality. We do not know the relative weights to give the different tobacco products, nor the length of the latent period before the tobacco factor exerts its effect—which Clemmesen believes may be as long as 30 years; nor do we know what proportion of the recorded increase in mortality is real. All that can reasonably be concluded is that changes in national smoking habits in Britain are such as would have been expected to result in an increased incidence of carcinoma of the lung; but whether they are adequate to account for the whole increase is uncertain.

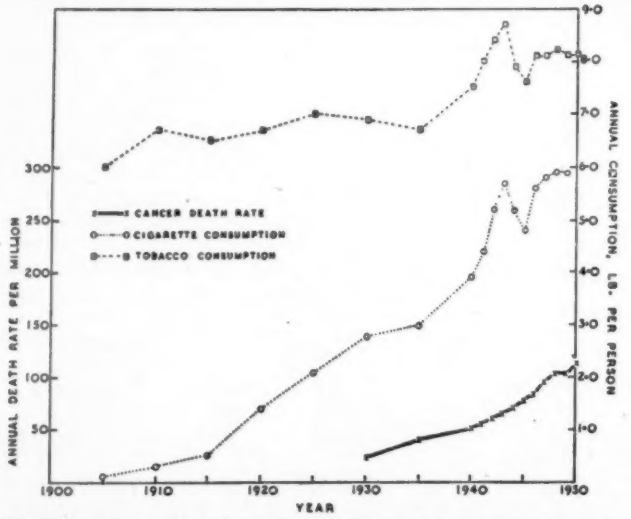


FIG. 8.—Death rate from lung cancer and consumption of cigarettes and of all tobacco, U.S.A. For cigarette and total tobacco consumption see Garner (1946); later figures provided by the Commercial Attaché of the American Embassy.

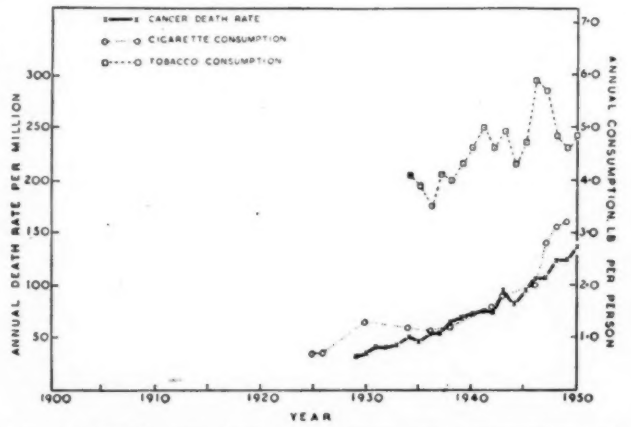


FIG. 9.—Death rate from lung cancer and consumption of cigarettes and of all tobacco, Switzerland. Statistics of cancer death rate and total tobacco consumption provided by Bureau Fédéral de Statistique, Berne; of cigarette consumption calculated from figures published by Gsell (1951).

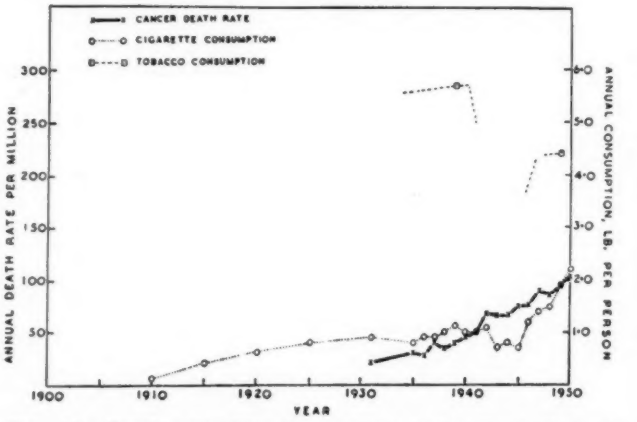


FIG. 10.—Death rate from lung cancer and consumption of cigarettes and of all tobacco, Denmark. For cancer death rate and cigarette consumption see Clemmesen, Nielsen, and Jensen (1953); for total tobacco consumption see "Anon." (1950).

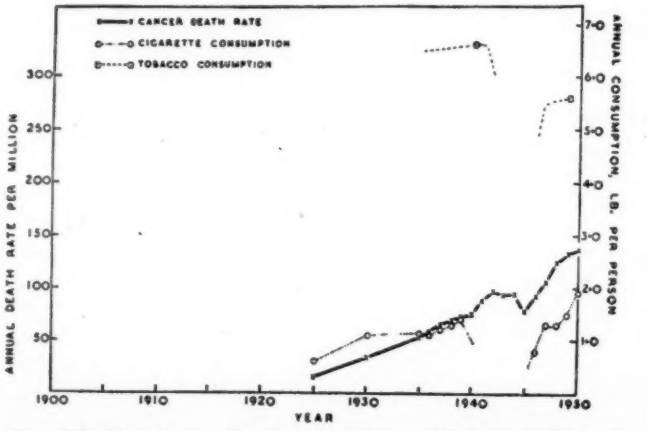


FIG. 11.—Death rate from lung cancer and consumption of cigarettes and of all tobacco, Holland. For cancer death rate and cigarette consumption see Kortweg (1953); for total tobacco consumption see "Anon." (1950).

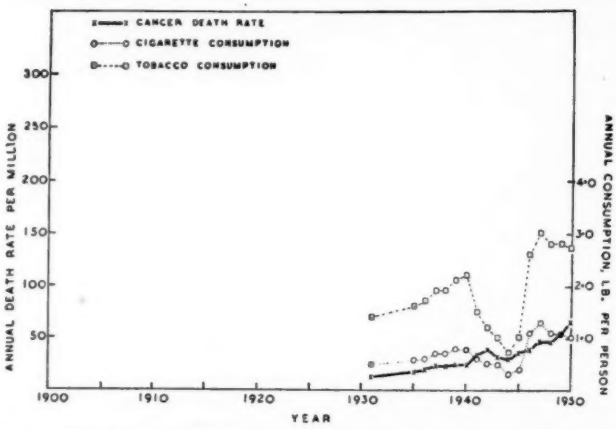


FIG. 12.—Death rate from lung cancer and consumption of cigarettes and of all tobacco, Norway. Statistics of cigarette and tobacco consumption provided by Professor L. Kreyberg (personal communication).

Attempts to relate mortality rates and tobacco consumption in different countries encounter the same difficulties. Estimates of the cigarette and total tobacco consumptions, together with the recorded mortality rates, for as far back as I have been able to obtain data, are shown in Figs. 8, 9, 10, 11, and 12 for the U.S.A., Switzerland, Denmark, Holland, and Norway. In each case mortality rates show a closer correspondence with cigarette consumption than with tobacco consumption. Falls in mortality occurred in Holland and in Norway towards the end of the war, shortly after there had been a great reduction in the consumption of tobacco; but it is difficult to believe that they are causally related to the fall in tobacco consumption, in view of the long latent period usually present in human cancer.

Fig. 13 shows the crude death rate in 1950 plotted against the average annual consumption of cigarettes per person over the preceding 20 years, for the six countries for which I have obtained data. I doubt whether much significance should be attached to the result, but it is not inconsistent with the existence of a relationship between lung cancer and cigarette-smoking. The mortality in England and Wales is, however, higher than would be expected, while in the U.S.A. it is lower.

It is a common observation that men smoke more than women, but it is not evident whether the difference in smoking habits is sufficient to account for the extent of the preponderance of men among subjects with the disease. The mortality rates which have been estimated for different levels of smoking among men and women in London suggest that sex differences still persist at each level (Doll and Hill, 1952). Women, however, did not start smoking at all until after the first world war, and trade statistics show that, although 22% of all tobacco was smoked by women in 1950, the proportion smoked by them 25 years earlier was only 2.5%. Consequently there must be a much greater difference in the total amounts smoked by men and women now in the cancer age than is revealed by the histories of their recent smoking habits. It would seem likely, therefore, that the rates which have been calculated for smokers of different average amounts are not truly comparable for men and for women. This objection does not apply to the rates which can be calculated for non-smokers, and I believe that it is within this group that the most proper comparison can be made. The estimated rates for each sex and for three age groups are shown in Table VI. In view of the smallness of the numbers from which the rates in the two extreme groups were calculated, the differences between the rates for each sex are quite insignificant. The implication of the results can be appreciated more clearly if the female rates—more reliable because derived from larger numbers—are used to calculate the numbers of non-smokers expected among the men with bronchial carcinoma who were interviewed; the expected number is then 6.1.* The number actually observed was 7. Despite the large total number of patients interviewed, the observed number of non-smokers is small, and it is not possible to dogmatize from the results. Nevertheless, the similarity of the observed and expected numbers is striking, and it seems probable that, save for smoking and exposure to certain industrial risks, the disease may affect men and women equally.

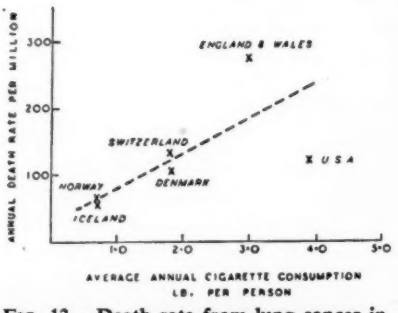


FIG. 13.—Death rate from lung cancer in 1950, and average cigarette consumption, 1931–50.

TABLE VI.—*Mortality from Lung Cancer among Non-smokers in Men and Women*

Age	Estimated Annual Death Rate per 1,000 Non-smokers		
	Men	Women	Persons
25–	0·03	0·02	0·02
45–	0·07	0·09	0·09
65–74	0·51	0·20	0·22

If this is so, and if, as has been suggested, the mortality among non-smokers is similar in town and country, death rates can be calculated for non-smokers of both sexes combined, which are based on reasonably sized numbers, and which, therefore, from this point of view justify some confidence. In submitting the rates I would, however, re-emphasize that the calculations are based on a number of fairly bold assumptions. The figures are therefore provisional, and it is recognized that the errors may be large. So long as this is borne in mind, it is of interest to use the rates to estimate the number of cases of lung cancer which would have been expected in England and Wales if none of the population had ever smoked. In 1950 the number between the ages of 25 and 74 would have been—in round figures—1,900; that is, 17% of the number which actually occurred.

No detailed figures are available to indicate the extent of the change in atmospheric pollution over the last half-century. The amount of coal consumed has varied little—from about 165 million to 190 million tons annually (Parker, 1950)—but the amount burnt efficiently in gasworks and electricity generating stations has increased enormously. It is likely, therefore, that there has actually been a decrease in smoke pollution, though not all the constituents of smoke will have decreased equally. The changes in mortality from lung cancer clearly cannot be attributed to changes in the amount of coal smoke in the atmosphere. Nor does there appear to be any reason why, if smoke is a responsible factor, men should be affected more than women.

To summarize, most of the known epidemiological facts about bronchial carcinoma are consistent with the effects of a limited number of industrial carcinogens and the presence of a carcinogenic substance in tobacco smoke—particularly in that derived from cigarettes. An exception may be the relatively low mortality from the disease in the U.S.A. Animal experiments confirm the carcinogenic potency of tobacco smoke, but the active agent has yet to be isolated. The position with regard to pollution of the atmosphere with chimney smoke is uncertain. The higher mortality in urban areas and the larger towns may perhaps be explicable on the grounds that cigarette-smoking has been heavier in these areas; on the other hand, as suggested by Stocks,

*The detailed calculations made in obtaining the expected number will be published elsewhere (Doll, 1953).

chimney smoke may be found to exacerbate the effect of the tobacco factor. Apart from certain mass radiography statistics, the meaning of which is difficult to assess, there is no epidemiological evidence to implicate pollution of the air with the exhaust fumes of cars or with road dust. Other weakly carcinogenic factors must, however, be postulated to account for a few remaining cases, evenly distributed among men and women and throughout town and country.

This year and next are centenaries of the great cholera epidemics in London, when the observations of Snow led to the realization that cholera was spread by water. I therefore make no apology for reminding you that it was purely statistical and epidemiological observations which provided the reasons for the measures which were responsible for the control of the disease. It is, however, with relief that I realize that measures of prevention are not within the scope of these lectures; for I have no desire to incur such a reaction as was expressed by *The Times* when it rejoiced over the fall of the first General Board of Health. "Aesculapius and Chiron," it said, " . . . have been deposed, and we prefer to take our chance of cholera and the rest than be bullied into health." The writer did indeed take his chance of cholera, which was raging in London within a month. But the chance was not to persist much longer. On the advice of the medical profession, led by such men as Sir John Simon, and concerned like Dr. Milroy to remedy "the neglect . . . of those laws of healthy existence with the consideration of which the science of Public Health professes to deal," the last major cholera epidemic in Britain was brought under control in 1866—seventeen years before Koch isolated the cholera vibrio. It may also prove that it will be unnecessary to await the isolation and identification of the specific active agent before steps can be taken to halt the rapid increase in the mortality from bronchial carcinoma and to turn it into an even more dramatic decline.

In concluding, I would like to acknowledge my indebtedness to Sir Ernest Kennaway for his encouragement and for the stimulation provided by his ideas; and to Professor Bradford Hill, not only for his constant advice, but also because so much of the work which has been referred to was his in origin, design, and execution.

My thanks are due to Mrs. Julie E. Backer (of the Central Bureau of Statistics, Oslo), Dr. J. Clemmesen, Mr. H. F. Dorn, Professor N. Dungal, Mr. A. Koller (Director of the Federal Bureau of Statistics, Berne), Dr. R. Korteweg, Professor L. Kreyberg, Dr. W. Logan, Dr. E. Pedersen, Dr. J. A. Scott, Mr. R. H. Thompson (of the Office of the Commercial Attaché, American Embassy), and Dr. G. Watkinson, for providing me with figures; and to Miss Freda Wadsworth and Mrs. Mary Young for drawing the diagrams.

REFERENCES

Andervont, H. B. (1937). *Publ. Hlth Rep., Wash.*, **52**, 1584.
"Anon." (1950). *J. roy. statist. Soc.*, **113**, 487.
Bidstrup, P. L. (1951). *Brit. J. industr. Med.*, **8**, 302.
Bonser, G. M. (1934). *J. Hyg., Lond.*, **34**, 218.
Brinton, H. P., Frasier, E. S., and Koven, A. L. (1952). *Publ. Hlth Rep., Wash.*, **67**, 835.
Brooks, W. D. W., Davidson, M., Thomas, C. P., Robson, K., and Smithers, D. W. (1951). *Thorax*, **6**, 1.
Bryson, C. C., and Spencer, H. (1951). *Quart. J. Med.*, n.s. **20**, 173.
Campbell, J. A. (1934). *Brit. J. exp. Path.*, **15**, 287.
—— (1936). Ibid., **17**, 146.
—— (1937). Ibid., **18**, 215.
Chief Inspector of Factories (1949). Ann. Rep. Chief Inspector of Factories and Workshops, 1948. H.M.S.O., London.
Clemmesen, J., and Busk, T. (1947). *Brit. J. Cancer*, **1**, 253.
—— Nielsen, A., and Jensen, E. (1953). Rep. C.I.O.M.S. Symposium on the Endemiology of Cancer of the Lung. *Acta Un. int. Cancr.*, in press.
Council for International Organizations of Medical Sciences (1953). Symposium on the Endemiology of Cancer of the Lung. *Acta Un. int. Cancr.*, in press.
Daff, M. E., Doll, R., and Kennaway, E. L. (1951). *Brit. J. Cancer*, **5**, 1.
—— and Kennaway, E. L. (1950). Ibid., **4**, 173.
Davies, J. N. P. (1948). *E. Afr. med. J.*, **25**, 117.
Dawson, K. B. (1952). *Brit. J. Cancer*, **6**, 22.
Doll, R. (1952). *Brit. J. industr. Med.*, **9**, 180.
—— (1953). *Brit. J. Cancer*. In press.
—— and Hill, A. B. (1950). *British Medical Journal*, **2**, 739.
—— —— (1952). Ibid., **2**, 1271.
Dublin, L. I., Spiegelman, M., and Leland, R. G. (1947). *Postgrad. Med.*, **2**, 188.
Dungal, N. (1950). *Lancet*, **2**, 245.
Essenberg, J. M. (1952). *Science*, **116**, 561.
Evans, R. D. (1950). *Acta Un. int. Cancr.*, **6**, 1229.
Flory, C. M. (1941). *Cancer Res.*, **1**, 262.
Fulton, J. S. (1949). *Proc. roy. Soc. Med.*, **42**, 775.
Garner, W. W. (1946). *The Production of Tobacco*. Blakiston, Philadelphia.
Gharpure, P. V. (1948). *Indian med. Gaz.*, **83**, 5.
Gloyne, S. R. (1951). *Lancet*, **1**, 810.
Goulden, F., Kennaway, E. L., and Urquhart, M. E. (1952). *Brit. J. Cancer*, **6**, 1.
Grady, H. G., and Stewart, H. L. (1940). *Amer. J. Path.*, **16**, 417.
Graham, E. A., Wynder, E. L., and Croninger, A. B. (1952). *Science*, **116**, 521.
Gsell, O. (1951). *Schweiz. med. Wschr.*, **81**, 662.
Haerting, F. H., and Hesse, W. (1879). *Vjschr. gerichtl. Med.*, **30**, 296; **31**, 102.
Heady, J. A., and Kennaway, E. L. (1949). *Brit. J. Cancer*, **3**, 311.
Hill, A. B., and Faning, E. L. (1948). *Brit. J. industr. Med.*, **5**, 1.
Hueper, W. C. (1952). *Tex. Rep. Biol. Med.*, **10**, 167.
Kennaway, E. L., and Kennaway, N. M. (1947). *Brit. J. Cancer*, **1**, 260.
Korteweg, R. (1951). Ibid., **5**, 21.
—— (1953). Rep. C.I.O.M.S. Symposium on the Endemiology of Cancer of the Lung. *Acta Un. int. Cancr.*, in press.
Kouwenaar, W. (1950). In Symposium on Geographical Pathology and Demography of Cancer. Council for the Co-ordination of International Congresses of Medical Sciences (World Health Organization and United Nations Educational, Scientific, and Cultural Organization).
Lange, K. (1935). *Z. Krebsforsch.*, **42**, 306.
Leiter, J., Shimkin, M. B., and Shear, M. J. (1942). *J. nat. Cancer Inst.*, **3**, 155.
Levin, M. I., Goldstein, H., and Gerhardt, P. R. (1950). *J. Amer. med. Ass.*, **143**, 336.
Lisco, H., and Finkel, H. P. (1949). *Fed. Proc.*, **8**, 360.
Lorenz, E., Stewart, H. L., Daniel, J. H., and Nelson, C. V. (1943). *Cancer Res.*, **3**, 123.
McConnell, R. B., Gordon, K. C. T., and Jones, T. (1952). *Lancet*, **2**, 651.
McDonald, S., and Woodhouse, D. L. (1942). *J. Path. Bact.*, **54**, 1.
Machle, W., and Gregorius, F. (1948). *Publ. Hlth Rep., Wash.*, **63**, 1114.
Mackay, D. (1951). Studies on Medical and Population Subjects, No. 4. General Register Office. H.M.S.O., London.
Mason, G. A. (1949). *Lancet*, **2**, 587.
Mills, C. A., and Porter, M. M. (1950). *Cancer Res.*, **10**, 539.
Miners' Phthisis Medical Bureau (1936). Report for the three years ended July 31, 1935. Union of South Africa Government Printers, Pretoria.
Müller, F. H. (1939). *Z. Krebsforsch.*, **49**, 57.
Nath, V., and Grewal, K. S. (1935). *Indian J. med. Res.*, **23**, 149.
Parker, A. (1950). *J. roy. Soc. Arts*, **99**, 85.
Passey, R. D., and Holmes, J. McD. (1935). *Quart. J. Med.*, n.s. **4**, 321.
Peller, S. (1939). *Human Biol.*, **11**, 130.
Perry, K., Bowler, R. G., Buckell, H. M., Druett, H. A., and Schilling, R. S. F. (1948). *Brit. J. industr. Med.*, **5**, 6.
Rigdon, R. H., and Kirchoff, H. (1951). *Sth. med. J.*, **44**, 506.
—— —— (1952). *Tex. Rep. Biol. Med.*, **10**, 76.
Sanders, E., Thomson, A. P., Cooper, E. A., and Lamb, F. W. M. (1932). *J. Hyg., Lond.*, **32**, 293.
Schairer, E., and Schöniger, E. (1943). *Z. Krebsforsch.*, **54**, 261.
Schrek, R., Baker, L. A., Ballard, G. P., and Dolgoff, S. (1950). *Cancer Res.*, **10**, 49.
Schwartz, P. (1950). *Beitr. Klin. Tuberk.*, **103**, 192.
Shaw, A. F. B. (1924). *Newc.-upon Tyne med. J.*, April, 1924. Quoted by W. E. M. Wardle, *Lancet*, 1951, **2**, 737.
Shik, R. G. (1946). *Amer. Rev. Soviet Med.*, **4**, 142.
Smith, W. E. (1950). *J. exp. Med.*, **91**, 87.
Steiner, P. E. (1944). *Arch. Path.*, **37**, 185.
—— Butt, E. M., and Edmondson, H. A. (1950). *J. nat. Cancer Inst.*, **11**, 497.
Stocks, P. (1950). Studies on Medical and Population Subjects, No. 3. General Register Office. H.M.S.O., London.
—— (1952). *Brit. J. Cancer*, **6**, 99.
Strachan, A. S. (1934). *J. Path. Bact.*, **39**, 209.
Turner, H. M., and Grace, H. G. (1938). *J. Hyg., Lond.*, **38**, 90.
—— and Martin, W. J. (1949). *British Medical Journal*, **2**, 1148.
Twort, J. M. (1939). *Sixteenth Annual Report of the British Empire Cancer Campaign*, p. 239.
Waller, R. E. (1952). *Brit. J. Cancer*, **6**, 8.
Wassink, W. F. (1948). *Ned. T. Geneesk.*, **92**, 3732.
Willis, R. A. (1948). *Pathology of Tumours*. Butterworth, London.
Woodruff, C. E., and Nahas, H. C. (1951). *Amer. Rev. Tuberc.*, **64**, 620.
—— Sen-Gupta, N. C., Wallace, S., Chapman, P. T., and Martineau, P. C. (1952). Ibid., **66**, 151.
Wynder, E. L., and Graham, E. A. (1950). *J. Amer. med. Ass.*, **143**, 329.
—— —— (1951). *Arch. industr. Hyg.*, **4**, 221.

The World Health Organization has approved a $25,000 supply programme to aid the victims of the recent earthquakes in the Ionian Islands. Supplies to be sent out, which are essentially to prevent epidemic diseases, will include water purifiers, tetanus prophylactics, rat poison, and galvanized piping. There is an estimated rat population of 100,000 in the islands, which could not only make serious inroads into food supplies but might rapidly spread disease. Dr. Duurt Rijkels, from the W.H.O. Regional Office in Europe, has recently returned from a visit to the affected areas made at the request of the Greek Government. He reports that the relief work is proceeding excellently, and the food supplies are now well organized. Many of those who were evacuated are returning home to repair their houses and to see to the grape harvest, which is expected to be very good this year.

THE APPROACH TO PSORIASIS*

BY

JOHN T. INGRAM, M.D., F.R.C.P.

Physician in Charge of Skin Department, General Infirmary at Leeds: Lecturer on Diseases of Skin, University of Leeds

The fact that psoriasis is compatible with good physical health and that it is not easily treated must account, in part, for the neglect it has suffered. The amazing and alarming advances in science and their application to medicine in this century have by-passed a number of important ills, of which psoriasis is one; but it remains something of a scourge, a curse to the afflicted and an offence to society. It is a common affection, difficult to move, unsightly and disfiguring, and, though it may often avoid exposed parts, it makes the sufferer something of an outcast, unable or unwilling to participate in a full and normally active life, and viewed askance by those who observe his affliction. He is often not appreciated even in the intimate circle of family and friends, where he may leave a trail of dust and scales. The "leper as white as snow" has been a wanderer through the pages of history, and it is little consolation to the psoriatic to say, with Hebra, that "psoriasis is a disease of the healthy." According to our modern conception of health it is indeed a serious disease, and with changing times it is desirable that the position should be repeatedly reviewed to seek some advance.

Research has not been lacking in this field, and was recently reviewed by Gans (1952), but was shown to have produced as yet little that was fruitful.

The cry has gone up in America that research into psoriasis should be organized and financed on a large scale similar to that devoted to such fields as rheumatism and cancer, but there is perhaps much that can be done on a more humble plane that might prepare the way.

What is the nature of the problem of psoriasis, and what can be done with our present knowledge and resources to relieve the position? We must admit to a great deal of ignorance, but without some reasonable hypothesis, based upon such knowledge as we have, there can be no advance.

A Constitutional Reaction

There have been many unsuccessful efforts to find a specific causative agent for psoriasis, but there can be little doubt that, in fact, psoriasis is a constitutional disorder. By that I mean that it is the expression of disturbed adjustment and adaptation as between the patient and his environment. This has nothing to do with allergy, which is a particular pattern of altered reaction to a specific stimulus or allergen and is cured by removal of the allergen. There is nothing to suggest that psoriasis is an allergic disease, and it is perhaps important to realize that. The poor response of psoriasis to cortisone and A.C.T.H. is interesting in this regard. This does not mean that allergic reactions may not occur in the psoriatic or in those subject to constitutional ills, but the allergic field does not embrace the constitutional, though the reverse may occur.

*British Medical Association Lecture delivered at Darlington on February 24, 1953.

Influence of Climate and Race

Constitutional disorders are personal and individual affairs, but they do tend to fall into certain groups, in relation to which it is common to find a central or primary sphere of maladjustment. Thus psychological, emotional, and nervous sensitiveness commonly form the core of eczematous ills. In psoriasis this central influence would seem to be the relationship of the patient to his climatic environment. The incidence of psoriasis is highest in the white races resident in temperate climates. Seasonal variation in psoriasis is common, and in general we may say that it tends to be worse in the winter and better in the summer. The incidence diminishes, in general, the warmer and less rigorous the climate—sun and warmth being the material considerations. This is obviously an important matter, and, other things being equal, it is usual for psoriasis to abate or clear if a patient moves into such suitable climate. Even in this country psoriasis is a more troublesome problem in the north than in the south, and in the north it will quite often affect exposed as well as covered parts.

This influence going on through the ages has no doubt become intimately bound up with racial factors, for there is undoubtedly some tendency to the inheritance of psoriasis even though the pattern of inheritance is not a simple one (Romanus, 1945). This factor may now, with the passage of time and movements of peoples, increasingly confuse the apparent incidence of psoriasis in different regions, but broadly we may say that while the white-skinned inhabitant of temperate climates is most susceptible—the greatest incidence of psoriasis is said to be in Iceland—the full-blooded negro, in his natural environment, is almost immune.

Psoriasis is a serious burden to our dermatological department in Leeds during the winter months, and this is probably the experience of most dermatological units in this country. Psoriasis, on the other hand, is less common in Australia, is uncommon in Indonesia, and is rarely seen in Kenya, Uganda, Nigeria, and similar climates, but it is not possible to gather accurate statistics, and a careful survey is desirable.

It has been reported that psoriasis in Jews of Western origin is seven times as common as psoriasis in Oriental Jews in Palestine, and this is an illustration of the way in which the movements of peoples, especially in the last century, may affect the natural incidence of the disease.

It would seem, however, that the essential disturbance in psoriasis does relate to geographical and climatic factors, and that to some extent these will have been imprinted upon the races found in those climates. What may be involved apart from temperature, humidity, and sunshine, we can only speculate, but it may well be that the characters of soil and water are not without effect.

Secondary Influences: Infective, Endocrine, Nervous

It is, however, a fact that, whatever the primary or central maladjustment in any constitutional ill, other secondary influences are important and may at times assume the predominant aetiological role. Any disturbance of health or tone, whether it arise from infection, from the ordinary physiological changes of puberty, pregnancy, and menopause, or from metabolic, psychological, or physical trauma, for instance, may evoke the pattern of reaction natural to the patient.

Thus in psoriasis we find that endocrine influences, especially those of puberty, pregnancy, and the menopause, and perhaps senility, are very potent provocations. In children acute infections, and particularly upper respiratory tract infections and fevers, almost invariably account for the acute generalized guttate attacks of psoriasis. It is relevant that upon occasion chronic infective foci are responsible for chronic psoriasis. Other most powerful influences, for both good and ill in psoriasis, are the emotional and nervous, and

these may also enter into what we regard as primarily endocrine influences. Evidences of such influence are constantly demonstrated to the dermatologist, and it cannot be doubted that the mere presence of psoriasis itself must exercise a morbid effect upon the mentality and outloook of most psoriatics, so that it is not difficult to realize how easily a vicious circle may arise in this field.

Some of these points are illustrated in a patient of mine who recently suffered her first attack of psoriasis after the age of 70, and as a result of the shock of her son having committed suicide by throwing himself out of the window. This patient's daughter had, however, suffered from psoriasis from puberty until her own second child was born when she was about 30 years of age. The psoriasis then suddenly disappeared, and has not yet recurred after fifteen years. This also illustrates the difficulty of obtaining a true family history of the disease.

As an important digression I would emphasize the seriousness from this angle of the attitude of the physician and nurse to psoriasis, the views they express before the patient, and particularly their reaction to the disease when it first appears or when the patient first presents himself. There is nothing so sad as the despondency of the psoriatic who has been assured that his ill is incurable, nothing so heartening and satisfying in medicine to physician and nurse as the patient who is cleared of his eruption in two or three weeks. If this happens with the first attack of psoriasis it may well determine the absence of relapse, but I have no doubt that chronicity and relapse can be as easily assured by the reverse approach.

Most dermatological patients are intelligent above the average, and even the problem of relapses is accepted and dealt with, provided the position is put clearly to them. There is great individual variation in this tendency to relapse.

The psoriatic reaction often overlaps such other constitutional dermatological responses as the eczematous, lichenoid, seborrhoeic, and various pustular conditions. In such phases psoriasis is often more difficult and intractable. Furthermore, it is not uncommon to observe the same patient presenting, at different times in his life, reactions which at one time are diagnosed with confidence as psoriasis or lichen or seborrhoeic dermatitis, and at other times as intermediate reactions, and again subsequently may present as a different single pattern of reaction. Different members of the same family may be subject to different reactions—one to psoriasis, another to eczema, and so on.

An Epidermal Reaction

To pass now from this consideration of the constitutional and non-allergic aspect of the problem of psoriasis to an appreciation of the site and significance of the reaction itself is profitable. Psoriasis occurs only in the human and not in other animals. It is primarily and essentially an epidermal reaction, and this may account for such distinctive features as the absolute demarcation of the lesions and of the erythema associated with the lesions, the absence of loss of hair, and the frequency of affection of the nails. It may also explain the poor response to cortisone and A.C.T.H., drugs which are particularly effective in mesenchymal diseases. It may explain the important role of local therapy in an affection that is essentially constitutional, and may account for the little effect of internal medication except by drugs, such as arsenic, which have an affinity for the epidermis.

The difficulty of moving a lesion of psoriasis from the skin has already been mentioned; it has literally to be burnt off, and it is strange that this fierce treatment rarely provokes or extends the affection as it would in most other skin diseases.

It is obviously significant that psoriasis does not normally occur on mucous membranes. It is also difficult to correlate this very common skin disease with general medical diseases affecting other organs in the body, and this again is strange. The only association that might suggest itself is that of the vague field of rheumatic disorders of joints and fibrous tissues, and this is of note, first because of the correlation of rheumatic ills with climatic considerations, and, secondly, because of the suggestive biomolecular relationship between keratin and collagen. But this cannot yet be described as more than a promising field for research, and it may be hoped that further attention to histochemical and biomolecular features of the psoriatic reaction may at least give some indication of the local mechanism of the disease (Astbury, 1950).

There is enough here to indicate that the problem of psoriasis is not quite as hopeless as our general ignorance might lead us to suppose. There are at least promising pointers for research into the effects of climatic influences on skin, and particularly upon the epidermis, and into racial and hereditary influences. The details of the physical and chemical aspects of the epidermal mechanism involved in this reaction should provide knowledge that must favour a better understanding of the nature of the disease and the proper approach to treatment.

Treatment

From what is known, however, the clinician can evolve some working hypothesis to guide him in the approach to management and treatment. It is at least possible in almost every case to clear the patient temporarily of his eruption in a matter of two or three weeks, and this knowledge is vitally important to the physician and the patient.

The problem of psoriasis, being a constitutional one, is always an individual problem, and calls for a general and not merely a dermatological approach. The appreciation of this is essential and fundamental to success. It is time-consuming, and may often seem unfruitful, but if this is not accepted and practised then all considerations which follow are of no significance. It is necessary to take a full and detailed medical history in relation to personal and family history, and every aspect of environmental influence. It is necessary to examine the patient thoroughly and not merely superficially. It is, in short, necessary for the physician to know his patient entirely and for the patient to know and to understand the physician's conception of his problem. It is not proposed here to pursue this further, but to pass to the local treatment of the psoriasis itself; yet it must be emphasized that the local is only one part of the treatment.

Because of the epidermal character of the disease local treatment is of more importance than in any other dermatosis except, perhaps xeroderma, lichen simplex, chronic lupus erythematosus, and cancer—where similar considerations arise. It is important also because it demands scrupulous care and accuracy and is effective only when so conducted, and because it is a valuable discipline to doctor, patient, and nurse. The practitioner must not only know and understand what he is doing here, not only instruct the patient and nurse accurately, but he must demonstrate what is done and must constantly check up to see that it is being done. In this matter of local treatment the skin is to be treated as one organ, and it is unprofitable to treat only a portion of the eruption.

The epidermis in these subjects settles naturally into the psoriatic habit and is not easily moved from it. It is undesirable to let the skin rest in this phase for fear of encouraging the habit and the spread of the habit to other parts of the skin. The presence of some psoriasis will encourage extension, especially if there is any constitutional disturbance. Complete and early clearance of an eruption favours a good prognosis.

The following has been the routine treatment in Leeds for about 20 years. In its complete form the patient for 10 minutes soaks and washes thoroughly in a bath of 20 gallons (90 litres) of water to which has been added 4 oz. (114 ml.) of coal-tar solution. After drying he is exposed to the ultraviolet mercury-vapour lamp, at first for half a minute at a

distance of 3 feet (0.9 metre), but the exposure time is increased to maintain a near-erythema dosage. The treatment is given daily.

Following the light treatment each lesion is obscured by the application of the paste :

Dithranol	..	..	2 gr. (0.13 g.)
Salicylic acid	..	..	10 gr. (0.65 g.)
Zinc oxide	..	..	120 gr. (8 g.)
Starch	..	..	120 gr. (8 g.)
Soft paraffin	..	to	1 oz. (31 g.)

This is allowed a few minutes to dry and may be powdered with talcum dusting powder. The patients are then covered with a stockinet sleeve dressing—making a vest, arms, and legs, which are tied at the shoulder and hip. They then dress and pursue their normal daily routine, to return for treatment again in 24 hours, when the dressing is removed and the procedure repeated (Figs. 1, 2, 3, and 4).

FIG. 1.—Psoriasis.

FIG. 2.—Psoriasis obscured by dithranol paste.

Several small points in this routine are to be emphasized. The physical characters of applications used on the skin are usually of more importance than the chemical ingredients they contain. It is to be stressed here that the dithranol paste must be dry and stiff, and for this purpose the paraffin base should have a melting point of 46° C. This is important, for paraffins are now pooled, and the melting-point may vary 20° C. or more between batches. If the paste is too soft it will not be effective.

Dithranol is an oxidizing agent, but in this paste it remains stable for months. As soon as it is applied to the skin, however, it is activated —presumably by skin secretions—and it rapidly and fiercely burns the part treated, making it red and inflamed and stained, and so removes the psoriasis. Here lies the importance of limiting the application to the psoriatic lesions and of not burning the normal skin, or the patient will be distressed and perhaps made ill.

The stockinet sleeve dressing acts like a compress and increases the intensity and efficacy of the treatment. If the daily bath is not taken the concentration in the skin rises and the reaction may be intensified, even to the extent of blistering in two or three days. This must, of course, be avoided.

The zinc paste cannot be applied to the hairy scalp, and here dithranol ointment *B.P.* may be used, or a mercury, salicylic, and tar ointment, or both. If these ointments are applied alternately, activation of the dithranol occurs on the scalp—but the combination of these drugs in a single ointment is not stable, and the dithranol is reduced in the course of a few days.

It is not difficult to appreciate when the psoriasis has been cleared, though this is often recognized by touch by the finger-tip more readily than by the eye, which is confused by the staining and reaction from the dithranol. Many patients clear within a week, though three weeks is a standard period of treatment for most. It is essential to be completely clear and not to leave a single active lesion.

The flexures are easily inflamed by the dithranol paste, and it should be applied to these sites for no more than one or two days ; the same is true for psoriasis of the face. The hands and feet are often more resistant, as are the lichenoid plaques sometimes encountered on palms, soles, sacrum, loin, and hips.

The treatment outlined is capable of infinite variation according to patient, site, circumstances, and facilities available, but the essentials remain.

Sometimes treatment is given every second day instead of daily, and this may be determined by pressure of work on the department or toughness of the psoriasis, so that a stronger reaction is tolerated. Usually the strength of the paste is reduced to ½ or 1 gr. to the ounce when treatment is not given daily. If very extensive, and especially if the psoriasis is shallow and of seborrhoeic type, a general application of a milder and softer paste is used. This procedure is much quicker and produces very little reaction :

Dithranol	½ gr. (32 mg.)
Salicylic acid	10 gr. (0.65 g.)
Zinc oxide	60 gr. (4 g.)
Starch	60 gr. (4 g.)
Soft paraffin	to 1 oz. (31 g.)

This may clear the affection or may leave some residual patches which have to be treated by the more vigorous application.

It is often possible to shorten the course and get better results by taking the patient into hospital for the period of treatment. On the other hand, good results can still be obtained by omitting the sunlight therapy and even omitting the tar from the bath, so bringing the treatment within the compass of home facilities.

FIG. 3.—Psoriasis covered with stockinet dressing.

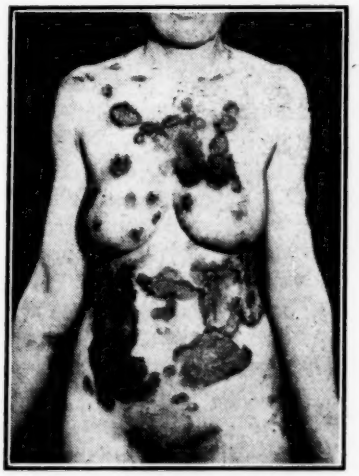


FIG. 4.—Dithranol reaction.

However, each feature of the regime has a purpose, so that the complete treatment has some advantage. The bath water penetrates the horny layer and softens the epidermis and makes it receptive of treatment ; the tar, apart from its value as an antipsoriatic measure, probably potentiates the subsequent light therapy ; and the light therapy introduces into the patient's environment something of those climatic

conditions which we believe to be influential in curing psoriasis. It is useful for the patient to receive a first course of treatment in a properly equipped hospital department so that the physician has more opportunity of observing and knowing his patient, and the patient is more efficiently trained in treatment.

Some of this treatment can be continued as maintenance and prophylactic therapy after psoriasis has cleared. Thus the daily bath with tar soap—even a tar bath occasionally—and regular care of the scalp, are desirable. The use of a pomade with mercury, salicylic acid, and tar on the scalp may be adopted as a routine toilet measure. A daily exposure to ultra-violet light is still more profitable, especially when taken after a bath or a tar bath. For this purpose the powerful hospital pattern of lamp is desirable, so that the treatment may take no more than one or two minutes, become part of the toilet routine, and not be a burden.

It is not suggested that this is the only local treatment for psoriasis, but in this climate it is rapidly effective in all but the occasional patient.

A Hospital Service for Psoriatic Patients

It is not unreasonable to suggest that a national health service should, under present circumstances, provide a service of treatment which should be made available for the patient for purposes of clearing attacks of psoriasis, if not for prophylaxis. There is a large psoriatic population in this country, numbering perhaps half a million, and the disability and discomfort involved must be considerable. Such a service should be the responsibility of regional hospital boards, who should provide, under the direction of their dermatologists, facilities for such treatment. It means the provision of baths and sunlight lamps, of nurses or orderlies trained to conduct treatment, and effective supervision; it means, further, a permanent staff, for the uninstructed nurse will not produce results.

Such a service would not only relieve a large number of patients of an intolerable burden, but would place under the constant eye of the dermatologists in the service a mass of clinical material—a circumstance that must favour an advance in our knowledge and encourage research. That fundamental research is necessary and essential to advancement in this field is not to be questioned. It is suggested that the expenditure of money on such services as have been outlined would be profitable to the community and is the proper function of a health service. It cannot be doubted that such a scheme in practice would inevitably stimulate useful research, both clinical and fundamental, and would provide the opportunities likely to make it purposeful and successful.

Summary

It is suggested that psoriasis is a constitutional disorder in which the fundamental maladjustment relates to climate.

There is a tendency for the disease to be inherited and so to be associated with some racial predisposition.

Though climatic influences are primary and fundamental, secondary influences, such as the infective, endocrine, and nervous, may assume major importance.

The significance of the epidermal character of the reaction is stressed, and fundamental research into the mechanism of the reaction is necessary.

Treatment can be rapidly effective in clearing the eruption, and a hospital service should be provided for the treatment of psoriasis under the health scheme.

Such a scheme, in addition to providing a necessary service to the community, would favour the pursuit of purposeful research, both clinical and fundamental.

REFERENCES

Astbury, W. T. (1950). *Brit. J. Derm. Syph.*, **62**, 1.
Gans, O. (1952) *Arch. Derm. Syph., Chicago*, **66**, 598.
Romanus, T. (1945). *Acta derm.-venereol., Stockh.*, **26**, Suppl. 12, 138.

URINARY STEROID EXCRETION IN RHEUMATOID ARTHRITIS

CHANGES IN KETONIC AND NON-KETONIC FRACTIONS DURING HORMONE THERAPY

BY

A. E. KELLIE, Ph.D.

AND

A. P. WADE, Ph.D.

(From the Courtauld Institute of Biochemistry, Middlesex Hospital Medical School, London)

In 1949 Hench, Kendall, Slocumb, and Polley reported that cortisone (17-hydroxy-11-dehydrocorticosterone) or A.C.T.H. (adrenocorticotropic hormone) would alleviate the symptoms of rheumatoid arthritis and of acute rheumatic fever. This observation stimulated inquiries into the role of the adrenal cortex and its hormones in normal metabolism and in relation to the aetiology of rheumatic conditions. Many workers have shown that A.C.T.H. is capable of stimulating the adrenal cortex to increased secretion, and that prolonged administration of A.C.T.H. or cortisone to man results in the development of the symptoms of Cushing's syndrome associated with increased excretion of steroids.

The present paper gives further details of the excretion of specific 17-ketosteroids following cortisone administration (Copeman *et al.*, 1952) and of work extended to include the administration of A.C.T.H. A new method of analysing the "non-ketonic" fraction has revealed changes following hormone therapy not previously reported.

Material

Urine samples (24-hour) were collected from normal persons (10 males and 10 pre-menopausal females) and from patients suffering from rheumatoid arthritis. The urine was preserved with chloroform, and, in the case of patients, collection was begun 12 days before treatment and continued throughout therapy. The urine was hydrolysed by boiling for 15 minutes with 3.3% hydrochloric acid and extracted with benzene. The neutral extract prepared by washing the benzene solution with 2N sodium hydroxide and water was fractionated by Girard T reagent into ketonic and non-ketonic steroids. Each of these fractions was divided into alcohols and non-alcohols (Dobriner, Lieberman, and Rhoads, 1948) as shown in Fig. 1.

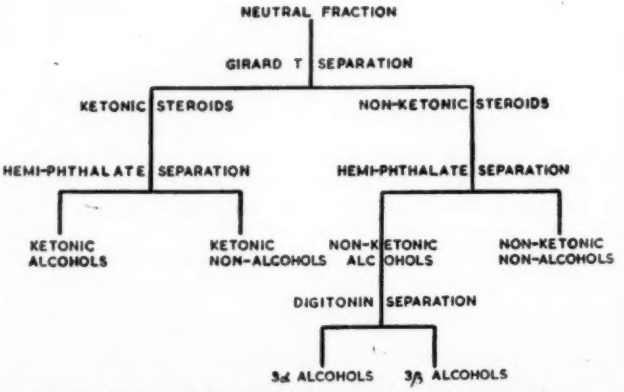


FIG. 1.—Scheme of separation of neutral steroid extracts.

The non-ketonic non-alcoholic fraction has not been shown to contain steroids and has not been further treated. The remaining fractions, two ketonic and two non-ketonic (3α and 3β alcohols), were analysed by chromatographic methods. The ketonic fraction was followed by a modification of the Dingemanse technique (Dingemanse, Huis in't Veld, and de Laat, 1946); the non-ketonic fraction by conversion of the component alcohols to 3 : 5 dinitrobenzoates (Kellie, Smith, and Wade, 1953; Kellie and Wade, 1953).

Comparison of Steroid Excretion in Normals and Rheumatoid Arthritics

Comparison of the steroid excretion of normal and arthritic individuals is possible both in respect of the composition of the neutral fraction and in that of the resulting subfractions. Table I shows the results of fractionating the urinary extracts of three cases of rheumatoid arthritis. The reduced excretion of both ketonic and non-ketonic material is revealed by comparison with the corresponding values for normal subjects.

Ketonic Alcohols.—Based upon the chromatographic analysis of the ketonic alcoholic fraction, Fig. 2 shows in graphical form a comparison of the excretion of individual steroids in normals and untreated arthritic persons. In each of several cases of rheumatoid arthritis analysed, the percentage of ketonic alcohols excreted as androsterone was much lower than in normal subjects (average values : arthritics, 18.7% ; normal subjects, 30%), whilst the percentage excreted as aetiocholanolone was generally higher (arthritics, 46% ; normal subjects, 38%). As a consequence the aetiocholanolone/androsterone ratio was higher in rheumatoid arthritis. The significance of this finding, if any, is not known. Robinson and Goulden (1949) observed a similar trend in cases of prostatic cancer.

Ketonic Non-alcohols.—The analysis of this fraction in several rheumatoid cases showed no departure from normal composition. The customary artifacts 3-β-chloro-Δ^{-5}-androstene-17-one and $\Delta^{-3 \text{ or } 5}$-androstene-17-one were present in reduced amounts, as reflected in the total fraction.

Non-ketonic (3α) *Alcohols.*—Based upon the results of the chromatographic analysis of the alcohol esters, Fig. 2 shows a comparison of the output of non-ketonic alcohols in rheumatoid arthritics as compared with that of normal persons. Work on the identity of the component alcohols of this fraction has not progressed sufficiently to be able to refer to them by name, but only by class. Urinary non-ketonic alcohols, following esterification with 3:5-dinitrobenzoyl chloride, separate readily on alumina into a series of fractions, here referred to by numbers I, II, III, etc., corresponding to increasing polarity of the eluents. Tentatively it is thought that fraction I consists of monohydroxy alcohols; fraction II of dihydroxy alcohols—for example, pregnanediol; fraction III of trihydroxy alcohols. The identity of the late fractions is still a matter of conjecture, but even in the absence of precise information it is possible to see that most fractions seem to be involved in the reduced excretion. The dihydroxy-alcohol fraction, normally the largest fraction, is substantially reduced. The amount of non-ketonic (3β) alcohols excreted in normal and rheumatoid arthritic individuals was negligible.

TABLE I.—*Fractionation of Urine Extracts—Normal and Rheumatoid Arthritic*

Fraction	Weight (mg./24 Hours)					Colorimetric Assay (mg./24 Hours)				
	Normal Subjects		Rheumatoid Arthritic Cases			Normal Subjects		Rheumatoid Arthritic Cases		
	(M)	(F)	1 (F)	2 (M)	3 (F)	(M)	(F)	1 (F)	2 (M)	3 (F)
Total neutral	66·4	56·8	16·0	36·4	28·8	13·5	10·6	4·2	4·3	4·0*
Ketonic	27·6	24·5	5·1	9·9	5·7	12·3	10·1	2·3	2·8	2·4*
Ketonic alcohols	13·5	10·0	3·1	4·0	4·4	8·8	6·3	1·6	1·9	1·5*
Ketonic non-alcohol	8·7	9·2	1·5	5·5	1·5	2·8	2·5	0·4	0·6	0·6*
Non-ketonic	25·5	24·4	7·5	12·4	10·5	—	—	—	—	—
Non-ketonic alcohol	8·6	6·6	3·2	8·8	7·4	18·8	16·0	8·4	13·1	9·9†

* Expressed as mg. equivalents of dehydroisoandrosterone. † Expressed as mg. equivalents of cholesterol.

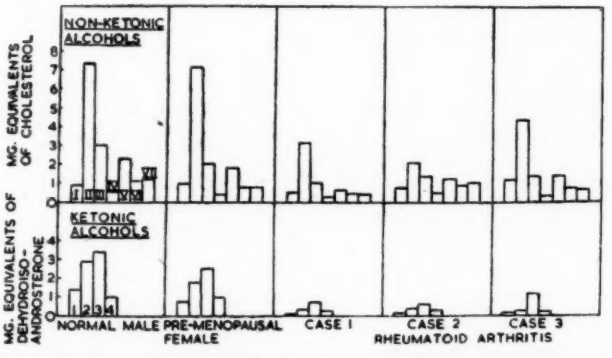


FIG. 2.—Excretion of steroids by normal persons and rheumatoid arthritics. I, monols; II, diols; III, triols, etc. 1, "β" compounds; 2, androsterone; 3, aetiocholanolone; 4, 11-oxygenated steroids.

Comparison of Excretion in Rheumatoid Arthritis Before and During A.C.T.H.

The subject, a female rheumatoid patient aged 49, received 560 mg. of A.C.T.H. over a period of fourteen days. The starting dose of 60 mg. on each of four days was progressively decreased until for the last four days a maintenance dose of 10 mg. was being given. This treatment caused a disappearance of clinical symptoms, and the 17-ketosteroid excretion rose from an average of 4.2 mg. a day to 10.8 mg. a day during treatment. The increase was maintained until the daily dose fell to 30 mg.; below this figure there was a steady decline in output. Table II gives the daily excretion of ketonic and non-ketonic material during treatment.

TABLE II.—*Fractionation of Urine Extracts Before and During A.C.T.H. (Female, 49 Years)*

Fraction	Weight (mg./24 Hours)		Colorimetric Assay (mg./24 Hours)	
	Before A.C.T.H.	During A.C.T.H.	Before A.C.T.H.	During A.C.T.H.
Total neutral	16·0	45·0	4·2	10·8*
Ketonic	5·1	21·6	2·3	10·3*
Ketonic alcohols	3·1	9·5	1·6	5·6*
Ketonic non-alcohols	1·5	4·3	0·4	1·2*
Non-ketonic	7·5	18·6	—	—
Non-ketonic alcohols	3·2	10·1	8·4	16·7†

* Expressed as mg. equivalents of dehydroisoandrosterone.
† Expressed as mg. equivalents of cholesterol.

The substantial increase in weight of material excreted daily following the administration of A.C.T.H. is reflected in all fractions. The increase in the ketonic fraction which has already been reported by many workers is shown to

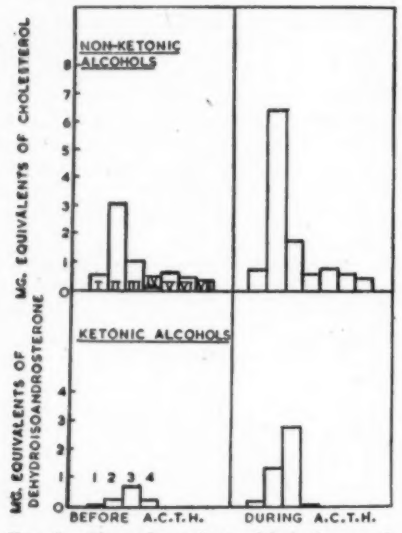


FIG. 3.—Excretion of steroids before and during A.C.T.H. I, monols; II, diols; III, triols, etc. 1, "β" compounds; 2, androsterone; 3, aetiocholanolone; 4, 11-oxygenated steroids.

affect both ketonic alcohols and, to a less extent, ketonic non-alcohols. The increase in the non-ketonic alcohols is also dramatic, but has not previously been reported.

Ketonic Alcohols.—Chromatography of this fraction following the administration of A.C.T.H. revealed no compounds not already normally present. The daily excretion figures shown graphically in Fig. 3, however, reveal that the increased excretion of total 17-ketosteroids is largely due to increased output of androsterone and aetiocholanolone. The aetiocholanolone/androsterone ratio was fairly constant—2.6:1 before and 2.0:1 during treatment—and did not restore the excretion pattern to normal. On the dose levels quoted only a very slight increase occurred in the excretion of 11-oxygenated steroids.

Non-ketonic Alcohols.—This fraction increased in weight about threefold during treatment. Fig. 3 shows the change in composition. Here again no information is yet available regarding the particular compounds responsible in fractions II, III, and V for the increase during treatment.

Comparison of Excretion in Rheumatoid Arthritis Before and During Cortisone

The patient, a woman aged 56, had a low initial excretion of 17-ketosteroids averaging 4 mg. a day over 11 pre-treatment days. Cortisone was given for a prolonged period, but urine collection was limited to the first 18 consecutive days of treatment, and during this period a total of 2.5 g. of cortisone was administered. The 17-ketosteroid excretion increased within 24 hours of starting treatment, but fluctuated greatly from day to day with no apparent relationship to the dose level. The average over a period of treatment was higher than pre-treatment level—5.7 mg. a day.

Fractionation of pre-treatment and treatment material showed that the small increase in total 17-ketosteroids was reflected in the ketonic alcohols. The weight of non-ketonic alcoholic material fell slightly (Table III).

TABLE III.—*Fractionation of Urine Extracts Before and During Cortisone (Female, 56 Years)*

Fraction	Weight (mg./24 Hours)		Colorimetric Assay (mg./24 Hours)	
	Before Cortisone	During Cortisone	Before Cortisone	During Cortisone
Total neutral	28·8	28·4	4·0	5·7*
Ketonic	5·7	8·0	2·4	4·0*
Ketonic alcohols ..	4·4	4·7	1·5	2·9*
Ketonic non-alcohols ..	1·5	2·6	0·6	0·7*
Non-ketonic	10·5	13·0	—	—
Non-ketonic alcohols ..	7·4	5·5	10·0	8·1†

* Expressed as mg. equivalents of dehydroisoandrosterone.
† Expressed as mg. equivalents of cholesterol.

Ketonic Alcohols.—Separation showed a slight fall in androsterone excretion, more than offset by a simultaneous rise in aetiocholanolone (Fig. 4). 11-Oxygenated steroids showed a noticeable increase, and from this fraction two crystalline compounds were isolated and identified by infra-red spectroscopy. Of these two compounds, 11-keto - aetiocholanolone and 11-hydroxy - aetiocholanolone, only the former is a component of normal urine. Both could arise as endogenous compounds or as metabolic products of administered cortisone, and it is not possible to decide between these alternatives in the present instance.

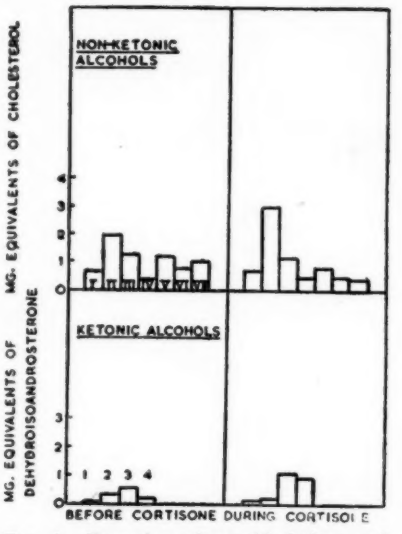


FIG. 4.—Excretion of steroids before and during cortisone. I, monols; II, diols; III, triols, etc. 1, "β" compounds; 2, androsterone; 3, aetiocholanolone; 4, 11-oxygenated steroids.

Non-ketonic Alcohols.—Although the total non-ketonic alcohols fell slightly during treatment, separation of the components (Fig. 4) showed that this was associated with a very small rise in fraction II (dihydroxy alcohols), offset by slight falls in most other fractions.

Comparison of A.C.T.H. and Cortisone Treatment in the Same Subject

The subject, a male patient aged 39 with rheumatoid arthritis, was studied by collecting urine samples throughout the following course of treatment:

(*a*) Pre-treatment	.. ..	11 days
(*b*) A.C.T.H.	.. ..	6 days, 100 mg. a day
(*c*) A.C.T.H.	.. ..	7 days, 300 mg. a day
(*d*) Rest period	.. ..	41 days
(*e*) Cortisone	.. ..	18 days, 100 mg. a day
(*f*) Cortisone and methyl-testosterone	.. ..	11 days, 100 mg. a day 25 mg. a day

The details of the 17-ketosteroid levels throughout treatment are summarized in Fig. 5. The first six days of A.C.T.H. treatment (100 mg. a day) led to no increase in 17-ketosteroid excretion, neither was there any significant clinical response. The dose was accordingly increased to 300 mg. a day, and was followed immediately by a rise in 17-ketosteroid output. The clinical response was such

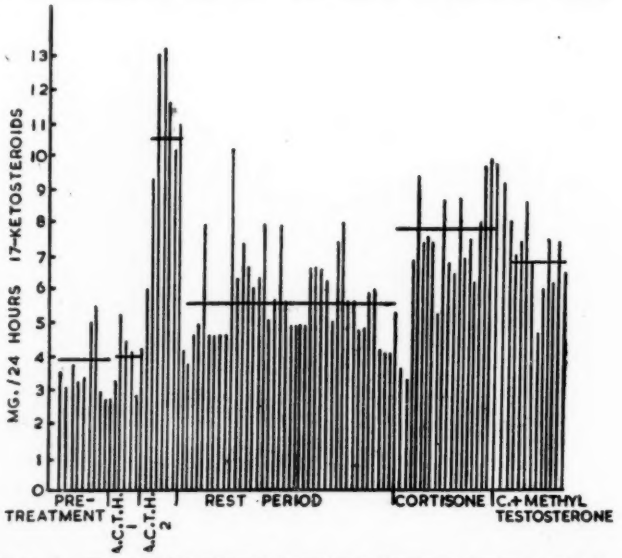


FIG. 5.—Total 17-ketosteroid excretion before and during A.C.T.H.

that after seven days it was necessary to stop treatment as the patient showed marked diabetic symptoms. After a prolonged rest period the administration of cortisone caused a rise in 17-ketosteroid output. The fractionation of the material (excluding the first A.C.T.H. treatment) is shown in Table IV, and the excretion patterns of the ketonic alcohols and non-ketonic alcohols are illustrated in Fig. 6.

TABLE IV.—*Fractionation of Urine Extracts—Treatment with A.C.T.H. and Cortisone (Male, 39 Years)*

Fraction	Colorimetric Assay (mg./24 Hours)				
	Pre-treatment	A.C.T.H. (300 mg./24 Hr.)	Rest Period	Cortisone	Cortisone and Methyl-testosterone
Total neutral ..	4·3	11·2	4·6	7·4	7·2*
Ketonic ..	2·8	8·8	3·8	6·8	6·0*
Ketonic alcoholic	1·9	6·1	2·4	4·9	5·3*
Ketonic non-alcoholic ..	0·6	1·3	0·7	1·3	1·1*
Non-ketonic alcoholic ..	13·1	24·9	10·4	10·0	18·5†

* Expressed as mg. equivalents of dehydroisoandrosterone.
† Expressed as mg. equivalents of cholesterol.

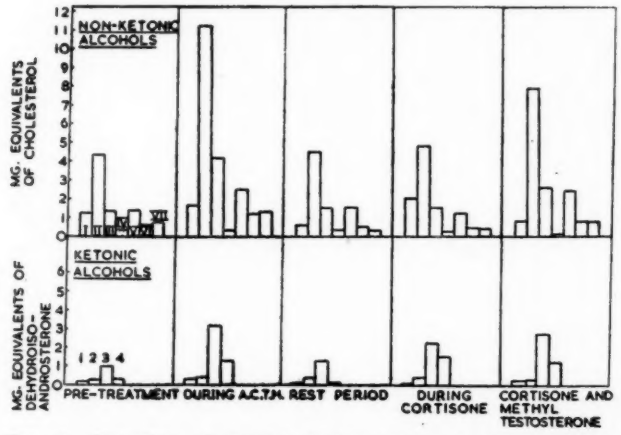


FIG. 6.—Excretion of steroids during treatment with A.C.T.H. and cortisone. I, monols; II, diols; III, triols, etc. 1, "β" compounds; 2, androsterone; 3, aetiocholanolone; 4, 11-oxygenated steroids.

As in the previous case, whilst A.C.T.H. produced an increase in both ketonic and non-ketonic fractions, the administration of cortisone caused a rise in the former fraction but little change in non-ketonic alcohols. Although the amount of aetiocholanolone changed during each period, expressed as a percentage, it remained remarkably constant. Addition of methyltestosterone to the administered cortisone produced no marked change in the ketonic fraction but almost doubled the weight of non-ketonic alcohols.

Treatment with A.C.T.H., although at a high dosage level, produced very little increase in androsterone, in contrast to the previous case, whilst the increase in aetiocholanolone and in the 11-oxygenated steroids was quite marked. The pronounced changes in the non-ketonic pattern are most apparent in fractions II, III, and V. During the rest period between the two sets of treatment the excretion patterns returned substantially to normal.

Cortisone treatment also caused very little increase in androsterone. The rise in aetiocholanolone was less and that of 11-oxygenated steroids greater than during A.C.T.H. therapy. The non-ketonic alcohol pattern was unaltered during treatment with cortisone alone, but changed considerably when methyltestosterone was also given.

Discussion

Comparison of the steroid excretion of rheumatoid arthritis patients with that of normal individuals has shown that the excretion of 17-ketonic alcohols and of non-ketonic alcohols in this condition is low. The excretion of androsterone, expressed as a percentage of total ketonic alcohols, was lower than in normals, whilst the percentage excreted as aetiocholanolone was generally higher. As a consequence the aetiocholanolone/androsterone ratio was higher in rheumatoid arthritics than in normal persons. This change has already been observed in at least one other pathological condition, and may have no specific bearing on steroid metabolism in rheumatoid arthritis.

Dobriner (1951a) reported the presence of 17-hydroxypregnanolone in the urine of four out of five cases of rheumatoid arthritis, although this compound is apparently absent from normal urine. It is not a 17-ketosteroid, and would not be revealed by the method used above unless present in excessive amounts, as, in the Zimmermann reaction, it gives approximately one-sixth of the colour intensity of a typical 17-ketone.

In the non-ketonic alcohols, fraction II, tentatively identified as the "dihydroxy alcohols," was decreased.

The changes in ketonic alcohols following A.C.T.H. and cortisone treatment have already been reported by others. A.C.T.H. caused a small increase in androsterone and 11-oxygenated steroids together with a substantial rise in aetiocholanolone excretion. After the administration of cortisone there was a greater increase in 11-oxygenated steroids and a substantial rise in aetiocholanolone. The latter finding is contrary to that of other workers, who found no increase in the excretion of androsterone and aetiocholanolone. Although Dobriner (1951b) has stated that the 11-oxygenated steroids do not contribute to the excretion of 11-deoxysteroids, the additional aetiocholanolone in these two cases must have come either from the administered cortisone or from some endogenous source.

Corresponding to the changes in the ketonic alcohols the output of non-ketonic alcohols increased greatly after A.C.T.H. administration. The main increase was observed in the "dihydroxy alcohol" fraction, but simultaneous increases were observed in other, as yet unidentified, fractions. In this connexion it is interesting to note that Nathanson, Engel, and Kelley (1951), following A.C.T.H. administration to a patient with multiple myeloma, observed an increase in total steroid alcohols. Paschkis (1951) also reported an increase in pregnanediol output following the administration of A.C.T.H. to men.

The administration of cortisone to rheumatoid arthritis patients had very little, if any, effect on the output of non-ketonic alcohols. In one case of Addison's disease treated intramuscularly with cortisone, Engel (1950) observed an increase in total and "non-ketonic" alcohols. Figures for the latter were obtained as a difference between total steroid alcohols and 17-ketosteroid values, and are not synonymous with non-ketonic alcohols as determined above, as they include ketonic steroids other than those substituted in the 17 position.

The addition of methyltestosterone (25 mg. daily for 11 days) to the administered cortisone, while having little effect on the ketonic steroids, greatly changed the excretion pattern of non-ketonic steroids. As treatment with cortisone for 18 days had failed to affect this fraction in either of the two cases, it is probable that the changes in excretion were a result of the added methyltestosterone. These changes may give a clue to the metabolic fate of methyl testosterone, about which little is known at present.

Summary

Steroid excretion has been studied in rheumatoid arthritic patients before and during treatment with A.C.T.H. and cortisone.

Changes in the excretion of 17-ketosteroids, already reported by others, have been largely confirmed. In contrast to the findings of other workers, an increase in aetiocholanolone excretion was observed during cortisone administration.

A.C.T.H. increased the excretion of total non-ketonic steroids. The increase was most pronounced in the dihydroxy steroid fraction.

Cortisone had little effect on non-ketonic alcohol excretion.

REFERENCES

Copeman, W. S. C., Savage, O., Bishop, P. M. F., Dodds, E. C., Kellie, A. E., Stewart, J. W., Glyn, J. H. H., Henly, A. A., and Tweed, J. M. (1952). *British Medical Journal*, 1, 397.
Dingemanse, E., Huis in't Veld, L. G., and de Laat, B. M. (1946). *J. clin. Endocr.*, 6, 535.
Dobriner, K. (1951a). *Bull. rheum. Dis.*, 2, 5.
—— (1951b). In *Steroids in Experimental and Clinical Practice*, edited by A. White. Churchill, London.
—— Lieberman, S., and Rhoads, C. P. (1948). *J. biol. Chem.*, 172, 241.
Engel, L. L. (1950). *Recent Progr. Hormone Res.*, 5, 335.
Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F. (1949). *Proc. Mayo Clin.*, 24, 181.
Kellie, A. E., Smith, E. R., and Wade, A. P. (1953). *Biochem. J.*, 53, 578
—— and Wade, A. P. (1953). Ibid., 53, 582.
Nathanson, I. T., Engel, L. L., and Kelley, R. M. (1951). *Proc. 2nd Clinical A.C.T.H. Conf.*, vol. 1. Churchill, London.
Paschkis, K. E. (1951). Ibid., vol. 1.
Robinson, A. M., and Goulden, F. (1949). *Brit. J. Cancer*, 3, 62.

POST-GASTRECTOMY SYNDROME

DEVIATION OF THE AFFERENT LOOP FROM THE GASTRO-INTESTINAL ANASTOMOSIS

BY

J. EWART SCHOFIELD, F.R.C.S.

Consulting Surgeon, Swindon and District Hospital Management Committee

AND

P. ST.G. ANDERSON, F.R.C.S.Ed.

Surgical Registrar, Swindon and District Hospital Management Committee

Much has been written recently about the early post-gastrectomy syndrome. This is not surprising when we consider in what large numbers the Polya type of operation of partial gastrectomy is being undertaken to-day for gastroduodenal ulceration. For the moment a new disease is being created, commonly referred to as the "dumping" or post-gastrectomy syndrome, consisting of symptoms varying in character and severity. The milder cases improve with the passage of time, but the severe ones remain, and it is with these that we are concerned. What is the extent of the dumping syndrome, and what happens to these patients? One so frequently hears that the syndrome occurs in only a small percentage of cases which often right themselves.

Custer, Butt, and Waugh (1946) thought that all but the mildest cases lasted indefinitely, and that the symptoms could be so severe and disabling as to warrant the use of the term "gastric cripple." Capper and Butler (1951), in examining the results of 558 Polya type of gastrectomies, found that 79 cases showed the early syndrome, and that 61 of these had symptoms lasting from two to eleven years. Goligher and Riley (1952) reported that six months after operation dumping occurred in 75% of their patients, which was severe in 12.5%, and that eighteen months after operation 47.5% still had dumping and 10% severe dumping. Others maintain that the percentage is not so high, but we suggest that a personal study of each post-gastrectomy patient will reveal some evidence of the syndrome in a large proportion of cases. The severe cases, by reason of their regular attendance at a follow-up clinic, can be most disconcerting and not at all helpful to other patients. When we consider the scale upon which the operation for peptic ulcer is being performed, the number of these unfortunate people must be large. Moreover, the operation is undertaken for men usually at the height of their wage-earning capacity and with a family to support. If, as a result of the dumping syndrome, they are unable to return to their pre-operation occupation, then the operation of gastrectomy cannot be regarded as a success.

This paper—a preliminary report—deals with the early post-gastrectomy syndrome following the Polya type of gastrectomy for duodenal ulcer. Our experience has been an average one, and, confronted by the problem of what to do for a small number of severe "dumpers," we decided to follow the procedure of Illingworth (quoted by Muir, 1949), who treated three cases successfully by lateral anastomosis of the efferent and afferent loops of the jejunum. Our patients readily accepted the opportunity of being rid of their miserable condition.

Lateral Anastomosis

In our series of antecolic Polya gastrectomies with a Hofmeister valve seven cases of persistent severe "dumping" occurred, which was very distressing both to the patients and to ourselves. These patients (five male, two female) were all submitted to an anastomosis between the efferent and afferent loops of the jejunum. Six had a gastrectomy for duodenal ulcer and one for a gastric ulcer. Their symptoms can be grouped conveniently under four headings:

1. *Vomiting Bile.*—All patients complained of this distressing symptom. Vomiting varied from one to three times a day, after food, and in amounts from 5 to 20 oz. (140 to 570 ml.) at a time.

2. *Vasomotor Symptoms.*—Four patients complained of severe sweating and dizziness after food, and had to lie down until the attack had passed off.

3. *Loss of Weight.*—Six cases lost amounts varying from 7 to 35 lb. (2.7 to 15.9 kg.).

4. *Vomiting Food.*—Three cases vomited food by itself or mixed with bile.

The onset of symptoms in all cases occurred within four weeks of discharge from hospital. All seven patients were emphatic that their symptoms were worse after the midday meal—that is, the big meal of the day.

Investigation of Cases.—A barium meal and a fractional test meal were carried out in all cases. The *x*-ray film showed afferent-loop filling and the fractional test meal a complete achlorhydria. Haematological investigations were all within normal limits.

Interval Between Operations.—The average interval was 15 months, the longest being two years and the shortest five months.

It is now about three years since these cases had their second operation, and their present condition can most conveniently be studied under the same headings as before:

1. *Vomiting Bile.*—This has been completely abolished in five cases. Two cases admit to an occasional vomit of bile every two or three weeks, but are greatly improved.

2. *Vasomotor Symptoms.*—These persisted in three out of the four cases affected, the fourth being completely free from symptoms. One case, in which the symptoms persisted, obtained relief by leaving the table and lying down.

3. *Loss of Weight.*—In five of the cases there was no gain in weight after entero-enterostomy; the other two were back to their pre-gastrectomy level and had gained 14 and 28 lb. (6.4 and 12.7 kg.).

4. *Vomiting Food.*—This was abolished in the three cases affected.

Six of the patients submitted to the operation were very satisfied with the result. One patient has undergone a further operation (see below). It would seem that the post-cibal vomiting was the most distressing symptom, as these patients were very glad to have this abolished and felt very much better in spite of the persisting vasomotor symptoms. Our conclusion from this short series was that,

whilst the lateral anastomosis improved all cases, it did not cure all the symptoms referable to dumping. We noted that, in spite of diverting the flow of bile from the stoma, no case has yet developed any signs of anastomotic ulcer.

Encouraged by these results, and believing that entero-anastomosis had relieved tension in the afferent loop, our interest became centred on this loop. In the recent literature nearly all writers discuss the afferent loop and the possible part it might play in the post-gastrectomy syndrome.

Lake (1948) drew attention to obstruction to the free passage of duodenal contents across the anastomosis which could occur, and might be a possible cause of symptoms. This condition, which has been called "afferent-loop stasis," is probably an accumulation of duodenal contents which eventually overcomes the obstruction at the anastomosis, so filling the gastric remnant. The contents are vomited in varying amounts, sometimes as much as a pint (570 ml.), after which the patient feels quite well and could settle down to another meal. McNealy (1942) estimated that 1.5 l. of secretion may be passed into the afferent loop in 24 hours. Mimpriss and Burt (1948) recognized the condition and added that as the food proceeds down the jejunum unmixed with bile and pancreatic juice there is a tendency to steatorrhoea. Tanner (1952) mentioned the need for a short afferent loop, which diminishes the chance of obstruction due to kinking and stasis in the loop. Illingworth, quoted by Muir (1949), faced with this problem, cured three cases with lateral anastomosis of the afferent and efferent loops. Wells and Welbourn (1951) devised the operation of jejunoplasty and treated three cases with excellent results. F. D. Murphy (1952, personal communication) considered that the afferent loop was responsible for the post-gastrectomy syndrome in some cases which he successfully treated by changing the Polya gastrectomy into the Billroth I type.

Mention should be made of the passage of food down the afferent loop so that it becomes mixed with bile, described as "afferent-loop reflux." The condition has been discussed by Mimpriss and Burt and by Wells and Welbourn. Mimpriss and Burt stated that the symptoms come on shortly after a meal, with distension, lassitude, nausea, vomiting, sweating, etc., but that it has occurred only with anastomosis of the afferent loop to the greater curvature. We have noted these symptoms in some of our cases in which the afferent loop has been anastomosed to the lesser curvature, and with a Hofmeister valve. It has been pointed out by Goligher and Riley (1952) and Butler and Capper (1951) that the clinical and radiological findings in afferent-loop reflux do not always coincide.

Attention to the weight of the afferent loop was drawn by Capper and Butler, who thought that the major factor in causing the syndrome was traction of a heavy afferent loop on the gastric remnant, plus the weight of the food. Emptying of the afferent loop greatly reduced the severity of the syndrome. In addition to reconstructing the peritoneal supports of the stomach, Capper and Butler also suture the afferent loop so that it is slung under the liver and the weight so taken off the gastric remnant.

The afferent loop therefore comes in for a good deal of criticism. We then considered whether its deviation from the gastro-intestinal anastomosis might decrease the incidence of the post-gastrectomy syndrome. This could be effected by a return to the Y-shaped anastomosis of Roux. At one time this form of gastro-jejunal anastomosis was in frequent use. It fell into disrepute in gastro-jejunostomy and in low partial gastrectomy because of the high incidence of anastomotic ulcer. Since these two operations failed materially to reduce the secretion of hydrochloric acid, this was not surprising. Warnings have been given against this type of anastomosis by Aird (1949) and Tanner (1952) amongst others. Maingot (1936, 1948) describes it as a most unsatisfactory operation for ulcer, and one which he has ceased to practise. In three cases of gastrectomy for anastomotic ulcer he employed the Y-shaped anastomosis, but all developed a recurrent ulcer. It should be conceded, however, that the Y-shaped anastomosis fell into disfavour at a time when the radical gastrectomy of to-day had not arrived. Now the operation demands an extensive resection of the acid-bearing area of the stomach, together with complete removal of the pyloric mucosa. In order to obtain an extensive and consistently uniform resection, we followed eventually the plan of the late Hedley Visick (1948) by mobilizing the stomach to the level of the first vas brevis.

We decided that in order to eliminate the afferent loop it was logical to employ the Y-shaped anastomosis in radical gastrectomy. An alternative way of doing this would be to perform a Billroth I operation. We have been impressed by the freedom from the post-gastrectomy syndrome in the latter operation, which we have performed for gastric ulcer. Capper and Butler found that the syndrome did not occur in 102 consecutive cases of Billroth I operation which they investigated. There is much evidence to support this view. However, we think it unwise to perform a Billroth I operation in cases of duodenal ulcer. Some of the duodenal ulcers which we have seen at operation would preclude a successful anastomosis between the duodenum and the gastric remnant. In many cases we feel that, in order to complete an anastomosis without tension, a principle of modern gastrectomy would have to be sacrificed—namely, the removal of enough of the acid-bearing area—and so incur the risk of recurrent ulceration.

Excision of the unhealthy portion of the duodenum, with adequate removal of the acid-bearing area, might result in an anastomosis under tension, with subsequent leakage. This was our unfortunate experience in one case, and on that account we have abandoned the Billroth I operation for duodenal ulcer. Tanner states that most surgeons prefer a gastro-jejunal anastomosis after gastrectomy for duodenal ulcer. Among the disadvantages of the Billroth I operation he mentions are: (1) utilization of a diseased organ for anastomosis; (2) to pass the ulcer a lengthy and hazardous dissection of the duodenum may be necessary; (3) scars may be left behind in the part of the duodenum retained; and (4) tendency to restrict the extent of the gastric resection in order to obtain a tension-free anastomosis.

Technique of Operation with Roux Anastomosis

The operation is proceeded with in the usual way to the stage when the duodenal stump is invaginated and the left gastric artery ligated. We would stress the importance of ligating this artery at its origin, so mobilizing the lesser curvature, and of leaving only one of the vasa brevia, which mobilizes the greater curvature; this allows a measured radical gastrectomy to be performed. Before preparing the jejunum for the Y-shaped anastomosis it should be realized that this will add 20 to 25 minutes to the time of the usual Polya gastrectomy. The jejunum is divided 18 in. (45 cm.) below the duodeno-jejunal flexure. It is unnecessary to ligate the vessels of the mesentery, as access can be gained through a bloodless jejunal window (see Fig. 1). The distal portion of the jejunum is closed,

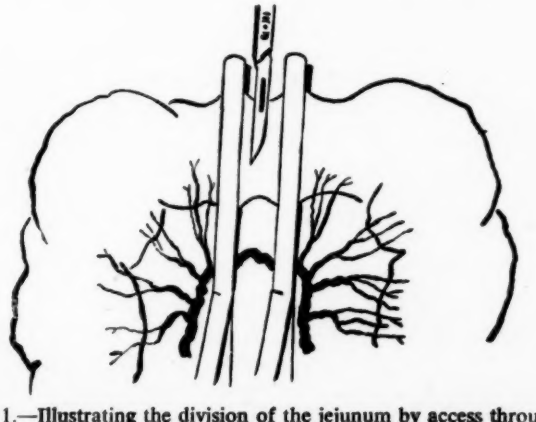


FIG. 1.—Illustrating the division of the jejunum by access through a jejunal window. The arterial arcade is not divided.

and the proximal portion is anastomosed to the side of the jejunum 12 in. (30 cm.) lower down. We have found that the anastomosis lies comfortably if the proximal jejunum is brought to lie on the left side. The jejunum is then anastomosed to the gastric remnant as in the usual Polya–Hofmeister anastomosis (see Fig. 2). We make a Hofmeister valve for the sole purpose of retaining the food for as long as possible in the stomach. The use of the Y-shaped anastomosis does not seem to add to the immediate mortality or morbidity rate of gastrectomy. Our cases have been followed up carefully, and a routine test-meal examination has been made three months after operation.

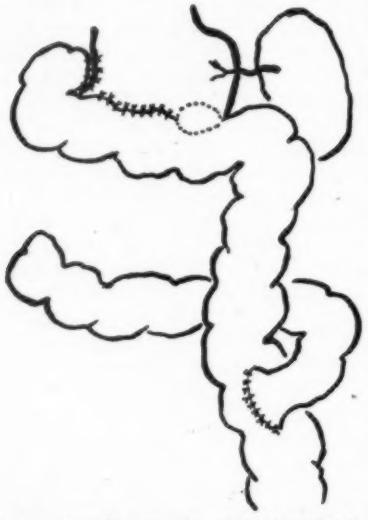


FIG. 2.—Illustrating the completed anastomosis.

At this stage two points incidental to the operation are worth mentioning. First, we find it particularly convenient to use a Y-shaped anastomosis when performing gastrectomy for gastro-jejunal ulcer. After division of the afferent and efferent loops of the jejunum, the fashioning of the Y anastomosis is a simple matter. Secondly, by deviation of the afferent loop, the duodenal contents pass uninterruptedly into the jejunum so that tension in the duodenum is relieved, with less likelihood of "blowing" of the duodenal stump. Two of our cases developed mild duodenal leaks with little inconvenience to the patients. We feel that, but for the Y-shaped anastomosis, duodenal tension might have been sufficient to produce an acute leakage, with possibly fatal results.

Discussion of Results

Accepting the principles of modern gastrectomy, we feel that the operation described above is based on sound logical premises. No doubt there will be much opposition to the reintroduction of this form of anastomosis from those surgeons who suffered a bitter experience in its use in the days of gastro-enterostomy and low gastrectomy. The lateral anastomosis, however, has already been used by Illingworth (Muir, 1949) to overcome the syndrome; and Wells and Welbourn (1951) have carried this operation a stage further in the same endeavour by introducing the operation of jejunoplasty. In surveying the results of this operation we ask ourselves two questions: Does this type of gastro-intestinal anastomosis increase the risk of anastomotic ulcer? and, What is the effect on the post-gastrectomy syndrome?

1. Recurrent Ulceration

Among 90 cases of duodenal ulcer treated by gastrectomy, with a Y-shaped anastomosis, 1 case of anastomotic ulcer has occurred. This was that of a man who before gastrectomy had suffered two perforations of a duodenal ulcer. His recurrent ulcer was a perforated anastomotic ulcer appearing three months after gastrectomy. Unfortunately, this patient developed a subphrenic abscess and died a few weeks later. This was one of our earlier cases, and it was after this setback that we paid very careful attention to the size of the gastric remnant and adhered rigidly to the measured radical gastrectomy. Whilst there is no accepted time-limit for recurrent ulcer, those surgeons who have had experience of gastro-enteric anastomosis in the days of gastro-enterostomy and low gastrectomy will recall that recurrent ulceration could occur in quite a short time. Most cases probably recurred within three years. Maingot (1952, personal communication) states that in his three cases, mentioned above, recurrent ulceration occurred within two years; one case recurred within three months. One of us (J. E. S.) has observed anastomotic ulcer following gastro-enterostomy and Devine's gastric occlusion operation in a number of cases within six months, and in one case a perforated anastomotic ulcer within 10 weeks. Since our cases are entering their third post-operative year it would seem fair to argue that by now we might have expected a number of recurrent ulcers among our 90 cases. Usually there is no mistaking the recurrent ulcer, the pain of which is severe and may show itself as an acute perforation or haematemesis.

Apart from the one case already mentioned, there is no hint of recurrent ulceration in any of our cases. This we regard as a matter of some importance, in that it goes a little way to substantiate the theory that the Y-shaped anastomosis does not increase the risk of recurrent ulcer after radical gastrectomy for duodenal ulcer. Recently, we encountered a duodenal ulcer so firmly fixed to the common bile duct that we performed gastrectomy with pre-pyloric section. Y-shaped anastomosis was not used. Six weeks later, when we performed a second operation for removal of the antrum, we found a large anastomotic ulcer perforated on to the diaphragm. A similar case is described by Tanner (1952). Such cases emphasize the speed at which an anastomotic ulcer can develop if the two important principles of gastric resection are not followed. Bathing of the anastomosis with the alkaline juices of the duodenum did not prevent recurrent ulcer in these cases.

Fractional test meals taken three months after gastrectomy show in nearly every case a complete absence of free hydrochloric acid. We are aware that the test meal is not altogether reliable, but, in the main, we are able to contrast the steeply rising curve of free hydrochloric acid in the pre-operative test with the constant straight line showing the absence of free hydrochloric acid in the post-operative test. Moreover, the usual fractional test meal performed after gastrectomy is sometimes complicated by the regurgitation of alkaline juices into the stomach and, therefore, is not a true index of the free hydrochloric acid. In our series regurgitation of bile cannot take place, and so we feel that the results are on that account more reliable.

2. Effect of Operation on Post-gastrectomy Syndrome

While we make no claim that the Y-shaped anastomosis is safe from recurrent ulceration, since time must elapse before this can be proved, nevertheless we are in a position to report on the effect of deviation of the afferent loop on the dumping syndrome. The food leaving the gastric remnant can take only one route, and the duodenal contents pass uninterrupted on their way into the jejunum. Therefore both afferent-loop regurgitation and reflux are prevented from taking place. Coincident with the prevention of the afferent-loop regurgitation it is interesting to note that we have not encountered a single case of intestinal "hurry." Furthermore, the post-operative loss of weight has, in most cases, been speedily regained. We feel this is due to the fact that the bile and the pancreatic juices are mixed with the food in its passage along the jejunum, and are not held up in the afferent loop, thus allowing normal absorption to take place.

What is the overall picture? It is a very striking one. All our patients have been interviewed carefully, and leading questions have been put to them in order to ascertain the slightest symptom. Attention has been given to vomiting, intestinal "hurry," failure to gain weight, vasomotor disturbances, and indeed the whole gamut of the dumping syndrome has been discussed with each individual. Apart from the discomfort experienced during the early post-operative period, it was difficult to persuade any patient to admit to any of the symptoms which have come to be included in the term "dumping." The only symptom to which anyone would admit was that after a heavy meal there might be a degree of epigastric discomfort. From this symptom after a heavy meal those of us still fortunate to retain our stomachs are not exempt. Finally, we have noted the cheerfulness of our patients, which we ascribe

to their freedom from symptoms, to their rapid convalescence, and to their return to their pre-operative occupation.

Since we found that the Y anastomosis was producing such uniformly good functional results we decided to convert the Polya gastrectomies in patients who complained of severe dumping symptoms to a Y anastomosis, rather than carry out a lateral anastomosis for them. This conversion is a simple technical procedure. We have so far subjected three cases to operation, and, although the time is very short since their operations, the results are worth consideration.

Case 1.—A man aged 29 had a partial gastrectomy for duodenal ulcer (Polya–Hofmeister antecolic procedure) in February, 1951. He remained well for eight months, but failed to regain his pre-operative weight. In November he began vomiting bile in quantities of up to one pint (570 ml.) twice a week either in the early morning or after his midday meal, the biggest meal of the day. His weight was 7 lb. (3.2 kg.) below his pre-operative weight. A test meal showed a complete achlorhydria, the blood picture was normal, and a barium meal showed filling of the afferent loop. In April, 1952, the anastomosis was altered to a Roux-en-Y. At operation a long afferent loop was found which was not dilated. Since operation he has gained 7 lb. (3.2 kg.) in weight, has eaten well, and there has been no vomiting or feeling of nausea.

Case 2.—A man aged 41 had a perforated duodenal ulcer in 1937 and 1943 which was treated by simple suture. In November, 1950, partial gastrectomy (Polya antecolic anastomosis with a Hofmeister valve) was performed. For sixteen months after operation he remained well, then began to vomit bile in large quantities. His weight was stationary and below his pre-gastrectomy level. He felt a dull ache in the epigastrium and complained of sweating and lassitude before vomiting. A test meal showed a complete achlorhydria, the blood picture was normal, and a barium meal showed afferent-loop filling. In June, 1952, his anastomosis was altered to a Roux-en-Y. Since this he has gained over 7 lb. (3.2 kg.) in weight, vomiting and vasomotor symptoms have completely disappeared, and his appetite has been excellent.

Case 3.—A married woman aged 47 had a partial gastrectomy (Polya antecolic anastomosis with a Hofmeister valve) in 1950 for duodenal ulcer. Six months later she complained of vomiting bile, dizziness, sweating, and loss of weight. In July, 1951, a lateral anastomosis between the afferent and efferent loops was performed. Following this she was well for three months and then her vasomotor symptoms alone recurred. She found that she could abolish these by eating in a recumbent position. Her weight was 21 lb. (9.5 kg.) below her pre-gastrectomy level. In July, 1952, a test meal showed a complete achlorhydria, the blood picture was normal, and the anastomosis was converted to a Roux-en-Y. When last seen, her appetite was improving, she had no attacks of dizziness or sweating after meals, and her weight was stationary.

These three cases are extremely interesting, as they help to confirm our view that the afferent loop is responsible for the symptoms of early dumping. Case 3 is one in which the symptoms were not satisfactorily cured by entero-anastomosis. The time since operation, we realize, is extremely short, but as we have encountered no early dumping symptoms in our series of Roux-en-Y anastomoses we anticipate that the complete relief which they have obtained will be permanent.

Many theories have been advanced to explain the early dumping syndrome, and it is interesting to compare these with our results. The suggestions that distension of the efferent loop is responsible, or that the higher the level of the transection of the stomach the greater the incidence of dumping, are not substantiated. Moreover, as all our anastomoses were anterior to the colon, we cannot agree with Ogilvie (1952), who suggests anterior colic anastomosis as a possible cause of "dumping."

The evidence we offer confirms the view that afferent-loop stasis and reflux play a part in the "dumping" syndrome, and lends support to the view of Capper and Butler (1951), who regard the weight of the afferent loop as contributory.

Some surgeons claim that the incidence of dumping can be reduced to a minimum by operations requiring special technique, aimed at directing the flow of food into the efferent loop. Is it that these operations, having one inherent fault—namely, an afferent loop—are unable to guarantee immunity from the post-gastrectomy syndrome?

Other surgeons, in an attempt to obtain a better functional result, have devised operations of a much more complicated character—for example, colonic replacement (Moroney, 1951) and jejunal replacement (Henley and Hudson, 1952). These operations, though not intentionally designed to avoid an afferent loop, nevertheless may owe their success to the very fact that they have done so, rather than to the premises on which they were based. As a remedial operation for the post-gastrectomy syndrome, Henley and Hudson seem to achieve, by means of a very complicated operation, the same beneficial results as are obtained from the simple Y-shaped anastomosis.

In conclusion, let it be restated that we make no claim for this operation. We feel, however, even at this stage, that the results on the dumping syndrome are worth recording. If time proves that this form of anastomosis renders the patient more liable to recurrent ulceration, then, however beneficial may be the effects on the dumping syndrome, the operation would have no place in surgery. We feel that the arguments in favour of this operation are based on sound logical premises and that the immediate results are sufficiently encouraging to warrant its continuation. We are optimistic enough to hope that, at a later date, we shall produce ample evidence in its support which has stood the test of time.

Summary

The view is expressed that a new disease is being created on a considerable scale called "dumping," following the frequent performance of the Polya type of gastrectomy for peptic ulcer.

Results of lateral anastomosis of afferent and efferent loops as a treatment in seven cases of dumping are recorded.

References in the recent literature to afferent-loop stasis, reflux, and weight of the afferent loop are quoted.

Reasons are advanced for the reintroduction of the Y-shaped anastomosis in the Polya type of gastrectomy.

Technical details of the operation are described.

Results of the operation in 90 cases are described in relation to recurrent ulceration and effect on post-gastrectomy syndrome.

No claim is yet made that the operation is as safe from recurrent ulceration as is the Polya anastomosis.

It is claimed that in none of our cases treated by the Y anastomosis has the post-gastrectomy syndrome occurred.

The effect of conversion of the Polya anastomosis to the Roux type in three cases of post-gastrectomy syndrome is described.

The results in our series are compared with the theories advanced on the aetiology of dumping.

We are indebted to Mr. R. Thexton for the illustrations.

BIBLIOGRAPHY

Aird, I. (1949). *Companion in Surgical Studies*, p. 635. Livingstone, Edinburgh.
Butler, T. J., and Capper, W. M. (1951). *British Medical Journal*, 1, 1177.
Capper, W. M., and Butler, T. J. (1951). *Ibid.*, 2, 265.
Custer, M. D., Butt, H. R., and Waugh, J. M. (1946). *Ann. Surg.*, 123, 410.
Goligher, J. C., and Riley, T. R. (1952). *Lancet*, 1, 630.
Henley, F. A., and Hudson, R. V. (1952). *Brit. J. Surg.*, 40, 118.
Lake, N. C. (1948). *British Medical Journal*, 1, 285.
McNealy, R. W. (1942). *Surgery*, 12, 207.
Maingot, R. (1936). *Post-Graduate Surgery*, 1, 387. Medical Publications, London.
—— (1948). *Abdominal Operations*, p. 421. Lewis, London.
Mimpriss, T. W., and Burt, St. J. M. C. (1948). *British Medical Journal*, 2, 1095.
Moroney, J. (1951). *Lancet*, 1, 993.
Muir, A. (1949). *Brit. J. Surg.*, 37, 165.
Ogilvie, Sir H. (1952). *British Medical Journal*, 2, 299.
Tanner, N. C. (1952). *Modern Trends in Gastroenterology*, edited by F. Avery Jones, p. 399. Butterworth, London.
Visick, A. Hedley (1948). *Lancet*, 1, 505.
Wells, C., and Wellbourn, R. (1951). *British Medical Journal*, 1, 546.

A RABBIT SERUM CONTAINING A SPECIFIC AGGLUTININ FOR THE RED CELLS OF THE NEWBORN

BY

ELIZABETH W. IKIN, B.Sc.
Senior Scientific Officer, Blood Group Reference Laboratory, London

H. LEHMANN, M.D., Ph.D., F.R.I.C.
Senior Lecturer in Chemical Pathology, St. Bartholomew's Hospital, London

AND

A. E. MOURANT, M.A., D.M., D.Phil.
Director, Blood Group Reference Laboratory, London

We have for some time, in collaboration with Dr. P. W. Hutton, of Mulago Hospital, Kampala, Uganda, been attempting to repeat the experiments of Schneider and Levin (1950) in which they obtained rabbit antisera giving specific agglutination of the erythrocytes of sickle-cell anaemia patients. These particular experiments have, so far, been inconclusive, but in view of the definite results reported below, which we have now obtained by the injection of foetal erythrocytes into rabbits, we hope to continue our investigation of the response to the injection of sickle-cell anaemia erythrocytes.

An outstanding finding reported by Schneider and Levin was that their antisera agglutinated the red cells of sickle-cell anaemia patients but not of sickle-cell trait carriers. One of the differences between these two is the presence in the former, but not in the latter, of an alkali-resistant haemoglobin, thought to be foetal haemoglobin (Singer, Chernoff, and Singer, 1951). It has now been shown that this alkali-resistant haemoglobin is antigenically indistinguishable from true foetal haemoglobin (Chernoff, 1953 ; Goodman and Campbell, 1953). Foetal haemoglobin is present in nearly all types of haemolytic anaemia, and its clinical importance is shown by Table I, reproduced from Itano (1953). This table was published before Chernoff or Goodman and Campbell reported the presence of traces of foetal haemoglobin even in normal adults and sickle-cell trait carriers.

TABLE I.—*Distribution of Different Haemoglobins (From Itano, 1953)*

Condition	Haemoglobin				
	a (Normal Adult)	b (Sickle Cell)	c	d	f (Normal Foetal)
Normal adult	+	−	−	−	−
,, newborn	+	−	−	−	+
Sickle-cell trait	+	+	−	−	−
,, ,, anaemia	−	+	−	−	+
Haemoglobin-c trait	+	−	+	−	−
Sickle-cell haemoglobin-c disease	−	+	+	−	±
Haemoglobin-d trait	+	−	−	+	−
Sickle-cell haemoglobin-d disease	−	+	−	+	+
Thalassaemia minor	+	−	−	−	±
,, major	+	−	−	−	+
Sickle-cell thalassaemia disease	+	+	−	−	+
Some acquired haemolytic anaemias	+	−	−	−	+

We are not in a position to assert that the serum of Schneider and Levin, which acts on the cells of sickle-cell anaemia but not on those of the sickle-cell trait, agglutinated specifically cells containing foetal haemoglobin, but a consideration of this possibility, and the fact that the one feature common to nearly all haemolytic anaemias is the presence of foetal haemoglobin in the red cells in appreciable quantity, led us to attempt to prepare a specific agglutinin for human foetal red cells. We considered that such an agglutinin might be of value in the investigation of haemolytic anaemias both of infants and of adults.

Preparation of Sera

Unclotted blood was obtained by syringe from the placental portion of the cord when on delivery the circulation between placenta and the newborn was interrupted. In most cases this was then allowed to clot and red cells were subsequently obtained by breaking up the clot with a glass rod. In some cases the blood was heparinized. In each case the red cells were washed five times with an ice-cold solution of 4% glucose and 0.18% sodium chloride. They were then suspended in the glucose-saline solution so that 1 ml. of the final suspension contained 0.3 ml. of packed cells. The suspension was stored at 4° C. in separate lots of 3–4 ml. each. Three adult rabbits were each inoculated intravenously with 0.8 ml. of the suspension on each of five consecutive days ; this treatment was repeated once every four to six weeks, and ten days after the last injection the rabbits were bled ; the blood was allowed to clot and the serum was removed. After inactivation at 55° C. for 30 minutes the serum was frozen and kept in that state until it was used for absorption and agglutination experiments. The sera of rabbits I, II, and III showed only little agglutinating power after the third course ; after the fourth course, however, there was an impressive rise in titre in the serum of rabbit II, and even more in that of rabbit III, but not in that of rabbit I ; rabbit I showed a rise of titre, however, after the fifth course. This communication deals only with the sera of rabbits II and III obtained after the fourth course.

As the unabsorbed sera showed virtually no anti-M agglutinin they were absorbed with adult human red cells of group A_1N. Serum II was diluted twenty times with isotonic saline and the diluted serum was absorbed with three-quarters of its volume of packed A_1N cells ; serum III was diluted ten times and absorbed with an equal volume of the cells. After this treatment adult human red cells were only slightly agglutinated (see Table II), which was attributed to the persistence of anti-human species agglutinin.

The absorbed sera were titrated against cord and infant blood cells, together with normal adult controls, so far as possible of the same ABO and MN groups. Other adult specimens were tested in order to eliminate possible effects of blood-group systems other than ABO and MN (Table II). Table II shows ABO, MN, and, in view of their irregular behaviour in infancy, also the Lewis blood groups for each individual. The rhesus groups for adults and infants respectively were as follows :—CCDee : 3, 3 ; CcDee : 5, 7 ; CcDEe : 3, 1 ; C^wcDEe : 1, 0 ; ccDEE : 0, 2 ; ccDee : 2, 0 ; ccddee : 4, 4. Ten of the adults and seven of the infants were positive for S. The titrations for P for adults and infants respectively were as follows :—+ + + : 6, 2 ; + + : 3, 1 ; + : 4, 9 ; − : 7, 8. There was one Lu^a positive in each group. Four of the infants were not tested for Kell and three not for Fy^a ; the results for adults and infants were :—Kell positive : 2, 1 ; Fy^a positive : 15, 9.

Titration Techniques

Saline Titration.—Serial twofold dilutions of the sera were carried out with isotonic saline, and an equal volume of 3 to 4% cell suspension in saline was added to the fluid in each tube. The tubes were incubated at 37° C. for two hours, and

Table II.—*Albumin Titration of Sera II and III against Adult, Cord, and Infant Cells. The Titres refer to the Dilution of the Serum before the Addition of an Equal Volume of Red-cell Suspension.*

No.		ABO	MN	Le^a	Le^b	Serum II Dilutions							Serum III Dilutions								
						1/20	1/40	1/80	1/160	1/320	1/640	1/1280	1/10	1/20	1/40	1/80	1/160	1/320	1/640	1/1280	1/2560	1/5120
1	Normal adult	O	M	−	+	4	2	1					3	1								
2	,, ,,	O	M	−	+	4	1						4	1								
3	,, ,,	O	MN	−	+	1	0						0	0								
4	,, ,,	O	MN	+	−	1	0						0	0								
5	,, ,,	O	MN	+	−	2	2	1					2	2	1							
6	,, ,,	O	MN	−	+	2	1						2	1	1							
7	,, ,,	O	MN	−	+	4	1						1	0								
8	,, ,,	O	N	+	−	2	1						1	0								
9	,, ,,	O	N	−	+	4	2	1					4	1								
10	,, ,,	O	N	−	+	2	1						2	2	1							
11	,, ,,	O	N	−	+	3	1						1	0								
12	,, ,,	A_1	M	−	+	0	0						0	0								
13	,, ,,	A_1	M	−	+	2	1						1	0								
14	,, ,,	A_1	MN	−	+	2	1						1	0								
15	,, ,,	A_1	MN	−	+	0	0						0	0								
16	,, ,,	A_1	N	−	+	2	2	1					2	2	1							
17	,, ,,	A_1	N	+	−	3	1						1	0	0							
18	,, ,,	A_2	M	−	+	0	0						1	0								
19	,, ,,	A_2	MN	−	+	1	1						0	0								
20	,, ,,	B	MN	−	+	2	0						1	0								
21	7 days ..	O	M	+	−	5	5	4	4	1			5	5	5	5	5	5	4	4	2	1
22	3 ,, ..	O	MN	+	+	5	5	4	4	2	1		5	5	5	5	5	5	4	4	2	1
23	Cord	O	MN	−	−	5	5	4	4	2	1		5	5	5	5	5	5	4	4	2	1
24	24 days ..	O	MN	+	−	5	5	4	4	2	1		5	5	5	5	5	5	4	3	1	
25	Cord	O	MN	−	−	5	5	4	2	1			5	5	5	5	5	5	4	4	2	1
26	12½ months ..	O	MN	−	−	3	1						3	1								
27	Cord	O	MN	−	−	5	4	4	4	2	1		5	5	5	5	5	5	4	2	1	
28	,, ...	O	N	+	−	5	4	4	4	2	1		5	5	5	5	5	4	3	2	1	
29	,, ...	O	N	−	−	5	5	4	2	1			5	5	5	5	5	4	4	2	1	
30	,, ...	O	N	−	−	5	5	5	4	2	1		5	5	5	5	5	4	2	0		
31	,, ...	O	N	+	−	5	5	4	2	1			5	5	5	5	4	4	2	1		
32	20 days ..	A_1	M	+	−	5	5	4	4	3	1		5	5	5	5	5	5	4	4	3	1
33	Cord	A_1	M	−	−	5	5	3	2	1			5	5	5	5	4	4	3	2	1	
34	4½ months ..	A_1	MN	−	−	4	1						4	1								
35	Cord	A_1	MN	−	−	5	5	4	3	1			5	5	5	5	4	4	3	2	1	
36	9 days ..	A_1	MN	+	−	5	5	4	4	2	1		5	5	5	5	5	5	4	4	2	1
37	7 ,, ..	A_1	MN	+	−	5	5	4	4	2	1		5	5	5	5	5	5	4	4	2	1
38	Cord	A_1	MN	−	−	5	4	4	4	2	1		5	5	5	5	5	4	2	1		
39	6 days ..	A_2	N	+	−	5	5	4	4	4	2	1	5	5	5	5	5	5	4	4	2	1
40	5 months ..	B	N	−	−	1	0						0	0								

0=All cells separate and evenly distributed. 1=A definite but weak reaction in which there is a uniform distribution of very small clumps of 4–6 cells. 2=Clumps of 8–12 cells. 3=Not quite such big clumps as in 4; numerous unagglutinated cells. 4=Granularity just visible to the naked eye; very big clumps under the microscope; some unagglutinated cells. 5=Numerous clumps, visible to the naked eye.

the cells transferred to a slide and examined microscopically. All titres so observed were very low, and there were no constant differences between the cord and infant cells and the adult controls. The results are therefore not reported in detail.

Indirect Coombs Test.—The cells were suspended in saline and incubated with saline dilutions of sera II and III; the cells were then washed three times with saline and mixed on a tile with suitably diluted goat anti-rabbit-globulin serum. The cord and infant bloods gave somewhat higher titres than the adult controls, but the differences were not great and hence are not reported in detail.

Albumin Titration.—Suspension of red cells in albumin solutions is not commonly used in agglutination experiments with animal sera; we decided to try this procedure, however, and found it to give satisfactory results. Serial two-fold dilutions of the absorbed rabbit serum were made with normal adult human AB serum, and to each volume of diluted serum was added an equal volume of a 5% suspension of red cells in 20% bovine albumin. Incubation was carried out for two hours at 37° C., and results were read microscopically after transfer to slides. This method showed considerable and systematic differences between the cord and infant cells on the one hand, and the adult control cells on the other. The results are shown in Table II.

TABLE III

Serum	Ratio Serum: Packed Cells	Absorption
II	1:0·75	Not detectable
II	1:1	Partial
II	1:1·25*	Complete
III	1:1	Not detectable
III	1:2	Partial
III	1:2·5†	Complete

* Absorption with 1 volume of cells, followed by 1/4 volume.
† Absorption with 2 volumes of cells, followed by 1/2 volume.

Absorption.—In view of the possibility that the cord blood cells were clumping because of something other than the presence of a specific antigen, possibly a major protein constituent of the serum, absorption experiments were carried out, using the red cells of cord blood 33 for the purpose. Serum II was diluted twenty times and serum III ten times with saline, and they were absorbed at 4° C. overnight, with varying volumes of packed cells, then tested for agglutinating power against fresh cells of the same type. The results are shown in Table III.

Discussion

Only in the albumin titrations were fully conclusive results obtained. The red cells from ten cord bloods and from seven infants below the age of 1 month were strongly agglutinated, while there was only slight agglutination, or none, of the red cells of 20 healthy adults and of three infants aged 4½, 5, and 12½ months. The agglutinin responsible was absorbed out by cord blood cells. The blood groups of the agglutinated bloods and of the controls are such that none of the known blood-group antigens or any combination of these could be responsible for the observed agglutinations. The Lewis system deserves special attention in this connexion, since there tend to be too few Le^b positives in the newborn and too many Le^a positives slightly later, as compared with adult blood groups. An inspection of the Lewis groups of the bloods (see Table II) shows, however, that this system is not responsible for the differences in agglutinability.

Agglutination is generally thought to be associated with the composition of the red-cell envelope and not of its contents, yet our findings suggest that the presence or absence of foetal haemoglobin may have been the determining factor in the agglutination and that the abnormal haemoglobin is associated with a similar abnormality of the lipo-protein of the cell envelope. Since our tests were completed the papers of Chernoff and of Goodman and Campbell have

reached us, reporting the preparation of sera which precipitate foetal haemoglobin specifically from aqueous solutions. The relation of these precipitins to our agglutinin remains to be determined. Chernoff reports that in one normal pregnant woman 2% of the total haemoglobin was present in the foetal form, whereas in twelve others the percentage was below 0.85, the upper limit in normal adults being 1.3. Since we have shown cord red cells to produce agglutinin in rabbits and the American authors have demonstrated foetal haemoglobin to be antigenic, it will be important to consider the possible consequences of transplacental introduction of such materials into the circulation of human mothers.

Summary

By the injection into rabbits of human cord blood cells, an antiserum has been prepared which agglutinates specifically the red cells of cord blood and of newborn infants.

We are grateful to Dr. R. R. A. Coombs for the supply of goat anti-rabbit-globulin serum and to the medical and nursing staff of the Department for Midwifery and Diseases of Women, St. Bartholomew's Hospital, for making available blood samples and helping in their collection. One of us (H. L.) thanks the Medical Research Council for a grant towards expenses.

REFERENCES

Chernoff, A. I. (1953). *Blood*, **8**, 399, 413.
Goodman, M., and Campbell, D. H. (1953). Ibid., **8**, 422.
Itano, H. A. (1953). *Science*, **117**, 89.
Schneider, R. G., and Levin, W. C. (1950). *Proc. Soc. exp. Biol. N.Y.*, **75**, 110.
Singer, K., Chernoff, A. I., and Singer, L. (1951). *Blood*, **6**, 413.

ALCOHOL-INDUCED PAIN IN HODGKIN'S DISEASE

BY

JAN G. de WINTER, M.D., D.M.R.

Consultant Radiotherapist, Brighton and Lewes Group Hospitals, Royal Sussex County Hospital, Brighton

Alcohol, when taken by patients with Hodgkin's disease, may in some cases give rise to severe pain. When present this symptom is of considerable clinical value—by focusing attention to areas of active disease, and by serving as a reliable guide when judging response to treatment. No mention is made of this curious intolerance to alcohol in any of the classical textbooks or monographs dealing with Hodgkin's disease, and no case report describing this symptom seems to have been published in this country so far. Only two references to this subject could be traced in the medical literature (Hoster, 1950; Verbeeten, 1952).* Hoster, in America, referring briefly to this phenomenon in one of his articles on Hodgkin's disease, states that in a number of his cases pain occurred or, if already present, was increased at the site of Hodgkin's deposits shortly after intake of alcohol-containing drinks, and that such pain was frequently replaced by localized anaesthesia if adequate amounts of alcohol were taken. Verbeeten, in Holland, quotes case histories of four patients with Hodgkin's disease (three male and one female) who suffered pain of such intensity after drinking alcohol that they all became teetotal. After *x*-ray therapy one of these patients was able to take alcohol again without ill-effects; no information is given on the fate of the other three cases.

*Since the submittance of this paper a similar report, describing nine cases, has been published by two Danish authors (Bichel, J., and Bastrup-Madsen, P., *Lancet*, 1953, **1**, 764).

In view of the scanty published data on the subject, the following two cases are placed on record.

Case 1

A housewife aged 37 was referred to hospital in February, 1951, with painless enlargement, for the past two years, of glands at the base of the neck which had suddenly begun to increase in size very rapidly during the previous month.

On examination she was found to be in excellent general health. The glands in the left posterior triangle were enlarged and there was a fixed mass, the size of a billiard ball, in the right supraclavicular fossa. Section of cervical glands showed Hodgkin's disease. An *x*-ray film of the chest showed enlargement of the right paratracheal glands. A course of *x*-ray therapy to cervical and supraclavicular areas as well as to the mediastinum was given in March, 1951, with resulting complete regression of all enlarged

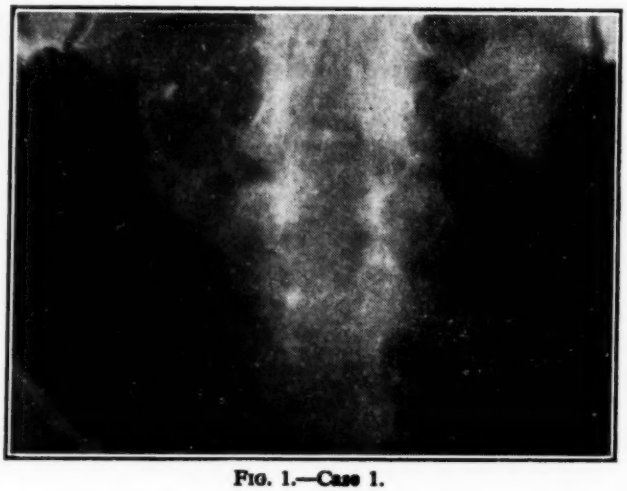


FIG. 1.—Case 1.

lymph nodes in the treated areas. She remained well until Christmas, 1951, when, on taking a small sherry, she experienced within a few minutes pain in the region of the coccyx on the left side which was so severe that she had to lie down. The acute pain passed within an hour or so, but the coccyx remained tender for three days. A week later, on New Year's Eve, she had only a few sips of sherry, which within a few minutes were again followed by most distressing pain in the region of the coccyx as before. When examined at the hospital on the following day there was marked tenderness on palpation in the left sacro-coccygeal region, but a radiograph of the coccyx at that time failed to reveal any definite bone disease. She was asked to have a sip of sherry in order to confirm the suspected relationship between pain and intake of alcohol. The resulting pain was so severe on this occasion that she decided to give up drinking alcohol altogether.

She remained well in herself throughout 1952, but continued to complain of slight tenderness on pressure in the left sacro-coccygeal region. She broke her 11 months' abstinence for the first time on December 9, 1952, when she had a cherry brandy. Within six minutes she was in terrible pain and "could not sit, stand, or walk." Finally, the severe pain was relieved by the patient lying in a hot bath. She was seen at the hospital within a week of this, and *x*-rayed again. Dr. Franklin reported as follows: "There is considerable bone destruction in the left sacro-coccygeal region, the appearances being consistent with the presence, in this region, of a lymphadenomatous deposit" (Fig. 1). A course of *x*-ray therapy to the affected left sacro-coccygeal region was started on December 31, and within two weeks the pain on taking alcohol was only very slight, and by the end of the three-weeks course she was able to take even large amounts of alcohol with impunity.

Case 2

A housewife and schoolteacher aged 25 was referred to hospital in July, 1952, with an indefinite history of lassitude and tightness in the chest of seven months' duration. She was unwell during this time, but it was only after taking alcohol that she really felt ill with pain in the chest and back. At first she did not connect the pain with alcohol, but during May and June the symptoms became so acute each time she took an alcoholic drink that she gave up drinking alcohol altogether.

On examination she appeared to be in good general health. She was dyspnoeic on exertion and the left upper zone was dull on percussion. There was an enlarged gland in the left supraclavicular fossa. Biopsy of the gland showed Hodgkin's disease. *X*-ray examination of the chest revealed a diffuse opacity filling the whole of the left upper zone and enlarged glands projecting laterally to the right from the upper mediastinum. A course of *x*-ray therapy to the mediastinum and left upper zone in July and August, 1952, was followed by excellent regression of all masses.

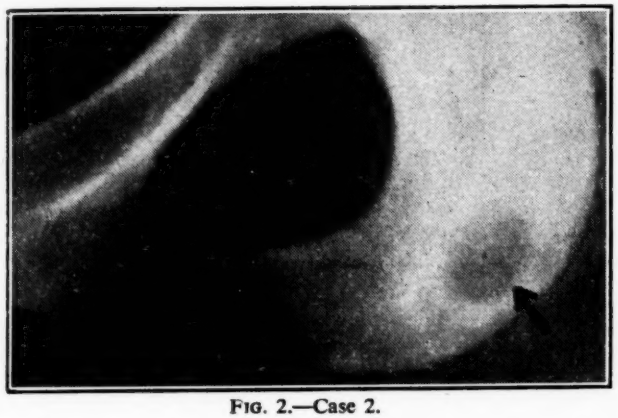


FIG. 2.—Case 2.

The patient took the first glass of sherry within one week of completion of treatment with no ill effects. For almost two months she was able to take alcohol with impunity. Then suddenly, in October, after a drink, she experienced acute pain in the region of the left buttock, and, after having a similarly painful experience on two more occasions, again gave up drinking alcohol. An *x*-ray film of the left ischium on November 17 showed the presence of an oval translucent area consistent with appearances of a lymphadenomatous deposit (Fig. 2). A course of *x*-ray therapy to the left ischium was given, and, as before, the patient was able to take alcoholic drinks without any ill effects within a week of completion of the treatment.

Discussion

In both cases alcohol produced localizing signs pinpointing, as it were, the site of active lymphadenomatous deposits in advance of clear-cut radiographic changes. Successful treatment, in both cases, was associated with instantaneous disappearance of symptoms which once more preceded the return to normal of radiographic appearances. Such individual hypersensitivity to alcohol, which seems to be confined to sufferers from Hodgkin's disease, is therefore of considerable clinical value as it may serve to betray the presence of active lymphadenoma at a time when the disease gives rise to few signs and so make possible early diagnosis and institution of appropriate treatment before symptoms become severe and unmistakable. The result of treatment in turn may be assessed by means of an alcoholic "test drink," a novel and probably not unwelcome form of investigation to the patient. It may prove useful to include such "diagnostic drinks" among the routine investigations carried out when following up cases of this type and to instruct the patients to report immediately should at any time intake of alcohol be followed by severe pain. What produces the pain in Hodgkin's disease, and whether it is due to localized oedema as suggested by Hoster (1950), is an intriguing question. So far there is nothing to suggest that alcohol has a deleterious effect on the course of Hodgkin's disease.

Thanks are due to Dr. Emily L. Franklin, senior consultant radiologist at this hospital, for the many *x*-ray reports, and to Mrs. K. Powell for translation of the Dutch paper. I am also indebted to Miss B. L. de Salis for the radiographs and to Miss L. J. Hunt for the photographic reproductions.

REFERENCES

Hoster, H. A. (1950). *Amer. J. Roentgenol.*, **64**, 915.
Verbeeten, B. (1952). *Ned. T. geneesk.*, **96**, 12.

FATAL ANAPHYLACTIC SHOCK DUE TO PENICILLIN

BY

FRANK J. PICK, M.D.
Clinical Pathologist, the Stafford Group of Hospitals

AND

JAMES F. PATTERSON, M.B., Ch.B.
General Practitioner

Allergic manifestations in reaction to various drugs have long been recognized and present a special problem to every physician. Recently antibiotics, and especially penicillin, have been added to the long list of these drugs, and penicillin, because of its wide application, plays a prominent part. The symptoms of sensitivity to penicillin are varied. Most frequent is an urticarial rash, but other skin lesions have been described. Sometimes a syndrome resembling serum sickness with urticaria, fever, oedema of mucous membranes, arthralgia, and lymphadenopathy appears (Wilensky, 1946; Humphreys, 1951; Wilkes, 1951). All these symptoms respond well to antihistamine drugs or adrenaline.

More serious reactions to procaine penicillin have been described by Batchelor *et al.* (1951) in patients undergoing treatment for the later stages of syphilis. The reaction developed immediately after intramuscular injection of 600,000–1,000,000 units of penicillin (five different preparations were involved), the patient experiencing a sensation of impending death (angor animi) and a feeling of prostration for several hours afterwards. There was no circulatory disturbance (pulse and blood pressure normal), respiratory embarrassment, or pain. They stress these facts in order to differentiate this reaction from a similar syndrome with a disturbance of circulation and angor animi associated with severe anaphylactoid reaction. On the other hand, several cases of non-fatal anaphylactic reactions after penicillin have been reported (O'Donovan and Klorfajn, 1946; Burleson, 1950; Mayer *et al.*, 1953), but few cases of sudden death following penicillin and attributed to hypersensitivity have been published.

The first fatal case recorded in Great Britain occurred in a 14-months-old healthy child who had been treated for burns and who died, five days after the penicillin treatment was begun, of cardiac tamponade due to serous effusion into the pericardium. There was also serous effusion into the pleural cavities. During the five days before death swelling of the face, pyrexia, and a diffuse skin rash occurred. The coroner recorded the cause of death as cardiac tamponade due to hypersensitivity to penicillin (*British Medical Journal*, 1951).

The second case published in Britain (Thomson, 1952) was that of a man aged 67 who had bougies passed under an "umbrella" of penicillin. He had had an alarming reaction one month previously after a course of penicillin injections, and he died ten to fifteen minutes after a later injection of penicillin, with symptoms described by the author as anaphylactic in nature.

In the United States, of the few reported cases of deaths due to penicillin hypersensitivity, Waldbott's (1949) case is of particular interest because of several features in common with the case reported below. The patient, a woman aged 39 who suffered from bronchial asthma and had had penicillin before, died almost immediately after receiving an intramuscular injection of penicillin during an acute attack of asthma. The symptoms preceding the fatal collapse were tightness in the nose and throat, swelling of the mouth, generalized itching, severe dyspnoea, and cyanosis. More recently another fatal case of anaphylactic shock has been published by Mayer *et al.* (1953). A man who had had repeated penicillin treatment for syphilis had a fainting turn after penicillin had been given three months before receiving the fatal dose. He complained of a peculiar pain in his chest immediately after the injection, and in a few minutes became comatose and died.

Case Report

A married woman aged 31 had suffered from bronchial asthma for two and a half years. A feature of the case was frequent association between respiratory infections and asthmatic attacks. In January, 1952, she was treated with penethamate ("estopen"; benzylpenicillin diethylaminoethylester hydriodide), 500,000 units daily, for four days and adrenaline hydrochloride as necessary. She had no unusual symptoms. During August she had a course of peptone injections. In the second week of December she developed another respiratory infection and again an attack of asthma. On December 11 she had 8 minims (0.5 ml.) of 1/1,000 solution of adrenaline hydrochloride with immediate relief from her asthma. Immediately following this 500,000 units of penethamate was given by intramuscular injection. Almost immediately she complained of a little headache and a feeling of faintness. Both these symptoms passed in a few minutes. The following day 500,000 units of penethamate and 0.75 ml. of hyperduric adrenaline were given. Five minutes later she complained of precordial pain, which lasted only several seconds. She appeared quite normal and conversed normally for a further five minutes, when she suddenly collapsed and lost consciousness. Respirations became gasping and infrequent, the pulse was rapid, but there was neither spasm nor convulsion. The intervals between respirations became longer, and she died after a few minutes.

Necropsy.—The pupils were dilated and the lips cyanosed. The brain showed no abnormality. The lungs were pale and inflated, and there were a few petechial haemorrhages beneath the posterior visceral pleura. The bronchi were dilated, and the bronchial mucosae thickened and congested and covered with mucus. Both chambers of the heart were contracted and empty. There were no other gross pathological changes. The cause of death accepted by the coroner was anaphylactic shock caused by penicillin in a case of bronchial asthma.

Discussion

As early as 1919 Cooke emphasized that hypersensitivity to drugs is an allergic reaction. Among 15 cases he found 3 with obvious manifestations of allergy, and there was a family history of allergy in the other 12. Waldbott's case was that of an asthmatic who after previous administration of penicillin developed urticaria, some aggravation of the asthma, joint pain, and fever. He had had experience of other cases of severe asthma occurring after initiation of the second or third course of penicillin. In Thomson's case there was a history of an alarming reaction to penicillin one month before the fatal dose.

All six cases reported by Mayer *et al.* received previous penicillin therapy and five gave a history of previous hypersensitivity to penicillin. Five of the patients, including one with a definite history of allergic manifestations, recovered from the anaphylactic shock and one died with symptoms almost identical with those of our case. That procaine cannot be blamed for these reactions was evident from the intradermal tests, which were positive to penicillin and negative to procaine in all cases in which they were done. Furthermore, the demonstration of passive transfer of circulating reagins to penicillin was successful in four out of five cases studied by Mayer *et al.*

There seems to be no doubt that any kind of penicillin can produce allergic reactions, and death has been reported after both crystalline and procaine penicillin. There is no predictable pattern in penicillin hypersensitivity reactions—several courses of penicillin may be symptomless before and even after severe allergic reactions. Nevertheless we should like to emphasize again the importance of careful inquiry for signs of previous allergic phenomena before penicillin is repeatedly administered to any patient, and special caution when dealing with allergic patients. In the presence of a history of allergy, skin-testing is indicated, and, if positive, further administration of penicillin should be avoided.

O'Donovan and Klorfajn succeeded in desensitizing their patient, but other authors doubt the possibility of successful desensitization. Burleson feels that diphenhydramine ("benadryl") hydrochloride (30 to 40 mg.) when given intravenously to his patient was a select and life-saving drug. Humphreys's patient was given adrenaline without any effect, but subcutaneous injection of mepyramine maleate ("anthisan"), 0.05 g., produced great relief.

In our case the simultaneous administration of adrenaline with the first injection of penicillin might have prevented severe reaction, and the fact that slow-acting hyperduric adrenaline was given with the second dose might have allowed the fatal reaction to take place.

Waldbott recommends intradermal testing in any allergic patient who had previous injections of penicillin in doses of 100 to 300 units and, if results are negative, in larger doses of 3,000 to 5,000 units intradermally 15 minutes later.

Summary

The trivial allergic reactions to penicillin are well known; the fact that fatal accidents occur is, however, not generally realized, and should certainly be emphasized in the light of the recent controversy on the abuse of antibiotics.

Death in anaphylactic shock due to penicillin hypersensitivity is described, and some of the relevant literature is reviewed and discussed.

References

Batchelor, R. C. L., *et al.* (1951). *Lancet*, **2**, 195.
British Medical Journal, 1951, **1**, 1269.
Burleson, R. J. (1950). *J. Amer. med. Ass.*, **142**, 562.
Cooke, R. A. (1919). Ibid., **73**, 759.
Humphreys, T. V. (1951). *British Medical Journal*, **1**, 299.
Mayer, P. S., *et al.* (1953). *J. Amer. med. Ass.*, **151**, 351.
O'Donovan, W. J., and Klorfajn, I. (1946). *Lancet*, **2**, 444.
Thomson, W. O. (1952). *British Medical Journal*, **2**, 70.
Waldbott, G. L. (1949). *J. Amer. med. Ass.*, **139**, 526.
Wilensky, A. O. (1946). Ibid., **131**, 1384.
Wilkes, H. M. (1951). *British Medical Journal*, **1**, 703.

The St. John Ambulance Association has recently published a booklet of instruction for air attendants, and issued regulations for a St. John Air Attendants' Course. The syllabus includes instruction on the effects of altitude on the human body, the selection of patients for travel by air, preparation and equipment for the flight, routine care of patients in flight, tropical medicine and hygiene and inoculations and vaccinations, and emergency midwifery.

LOCAL INFECTION WITH PASTEURELLA SEPTICA FOLLOWING A DOG-BITE

BY

D. F. V. BRUNSDON, M.B., B.S.
Registrar, Department of Clinical Pathology, Guy's Hospital

AND

B. L. MALLETT, M.B., B.S.
Out-Patient Officer, Guy's Hospital

Pasteurellosis is commonly seen in animals and birds but rarely diagnosed in man. Cats and rabbits seem to have been responsible for most human cases (Schipper, 1947), and, despite the frequent occurrence of pasteurellae in the saliva of healthy dogs, only three cases of human infection following a dog-bite have been reported (Allott *et al.*, 1944). A further case is now recorded.

Clinical History

A boy aged 9 was bitten by a dog on September 10, 1952. Three inches above the right medial malleolus there was a clean gaping laceration of the skin and subcutaneous tissues, 1½ in. (3.8 cm.) long. Routine wound toilet was carried out, the wound sutured, and A.T.S., 750 units, given intramuscularly.

On September 16 infection was present with oedema and discoloration of the wound edges. An intramuscular injection of 300,000 units of procaine penicillin was given daily for three days, and the sutures were removed. The wound failed to heal, and a swab taken on September 17 yielded a pure growth of *Pasteurella septica*.

Sulphadimidine by mouth (1.5 g. at once and 1 g. six-hourly) was begun on September 23 and continued for five days. The boy's temperature rose on two occasions to 99.2° F. (37.3° C.), but he remained well. *X*-ray films of the right tibia showed no bony change in the region of the bite. The wound, following the course of sulphadimidine, became dry and granular but showed little tendency to re-epithelize, so that split-skin grafting was undertaken on October 15. Oral sulphadimidine was given for five days. Healing was complete 68 days after the bite was sustained.

Bacteriology

Wound swabs taken from the patient on September 17 and 23 grew a pure culture of a non-motile Gram-negative coccobacillus identified as *P. septica*. This organism showed bipolar staining with methylene blue, and capsules were present in preparations made from the peritoneal exudate of injected mice. The organisms grew best under aerobic conditions, and on blood agar produced low convex colonies 1.5 mm. in diameter with an entire edge. The colonies were clear peripherally with a greyish-white centre and a smooth shiny surface. They were butyrous in consistency and were readily emulsified. On MacConkey medium there was no visible growth after seven days' incubation at 37° C.

Biochemical Reactions.—The following carbohydrates were fermented without gas production: glucose, maltose, saccharose, raffinose, galactose, and trehalose. L.M., no change; indole, +; M.R., −; V.P., −; H_2S produced in small quantities; catalase, +; methylene blue reduction, +; NH_3 production, +; nitrate reduction, +. With the disk technique (Thompson, 1950) the organism was sensitive to penicillin, streptomycin, aureomycin, and chloramphenicol. It was also sensitive to sulphadimidine, 10 mg. per 100 ml.

Serology.—No antibodies could be demonstrated in serum obtained from the patient on October 1 and 8. Serological study of the organism was kindly undertaken by Mr. J. E. Smith, of the Department of Pathology, the Royal Veterinary College, London, who found that sera prepared against *P. septica* types most commonly found in healthy dogs agglutinated the isolated strain, while sera prepared against other *P. septica* types failed to do so. Six sera from healthy dogs agglutinated the isolated strain to the titre expected from previous work on agglutinin levels in healthy dogs against dog strains.

Discussion

This is one of 90 cases of dog-bite (in 10,179 accident cases) seen at Guy's Hospital casualty department during the period January 1 to November 15, 1952. Fourteen of these dog-bites showed evidence of infection, and in four healing was delayed beyond a fortnight, the longest to 40 days.

The wound in the present case appeared clean, with non-bevelled edges, and was treated by primary suture without excision—an omission not justified by subsequent events.

In view of the reports of underlying bony disease associated with wound infection with *P. septica* (Allott *et al.*, 1944; Cooper and Moore, 1945) *x*-ray films were taken of the right tibia. These showed no evidence of osteitis.

According to J. E. Smith (personal communication) the isolated strain is similar in its sugar-fermentation reactions and, antigenically, to strains commonly found in the saliva of healthy dogs, and it is surprising that human infection following dog-bite is rarely reported. Information has been obtained from the director of the Public Health Laboratory Service that, in the laboratories of his service, during the past two years *P. septica* has been isolated from dog-bite wounds on a number of occasions. This suggests that the condition might be discovered more often by routine swabbing of all dog-bites.

Summary

A case of local infection with *P. septica* following a dog-bite is reported.

The infecting strain proved to be of a type commonly found in the saliva of healthy dogs.

It is suggested that routine swabbing of dog-bites might show that infection with *P. septica* occurs more commonly than is generally realized.

Our thanks are due to Dr. F. A. Knott and Mr. P. W. Clarkson for permission to publish this case and for their encouragement and advice, and Mr. J. E. Smith, of the Department of Pathology, Royal Veterinary College, Camden Town, for his serological investigation of the *P. septica* strains.

REFERENCES

Allott, E. N., Cruickshank, R., Cyrias-Williams, R., Glass, V., Meyer, I. H., Straker, E. A., and Tee, G. (1944). *J. Path. Bact.*, **56**, 411.
Cooper, T. V., and Moore, B. (1945). *Lancet*, **1**, 753.
Schipper, G. J. (1947). *Bull. Johns Hopk. Hosp.*, **81**, 333.
Thompson, B. A. (1950). *J. clin. Path.*, **3**, 118.

Medical Memorandum

The Age of the Menarche in the Tropics

When Ellis (1950) summarized recent studies on the age of onset of menstruation in various climates he mentioned the difficulties inherent in obtaining accurate data in tropical countries. His own reliable observations in the hot moist climate of Lagos City, Southern Nigeria, did not confirm the widely held belief that children in the Tropics mature early.

We have been able to augment our earlier studies of the age of the menarche in English children (Wilson and Sutherland, 1950b) with data carefully collected in schools in Northern Nigeria, Central India (C. Thomson, 1952, personal communication), and Ceylon (Wilson and Sutherland, 1950a). These areas all lie between latitudes 5 and 20 degrees N., and the observations relate with one exception to homogeneous racial groups. As in England, each girl was asked simply for her present age and whether or not her periods had started. From the replies the average age of

Age of Attainment of the Menarche in Nigeria, Central India, and Ceylon Compared with Southern England

Group	No. of Children	Age of the Menarche	
		Mean Age in Years	Standard Deviation of Age in Years
Southern Nigeria (Ellis, 1950): Ibo and Yoruba:			
Series 1	300	14·22	1·00
,, 2	142	14·40	Not available
Northern Nigeria:			
Plateau pagans	74	14·50	1·24
Northern girls at school ..	172	14·14	0·61
Central India (Thomson, 1952): Aboriginals: Munda, Oraon, Santal	411	14·65	1·55
Ceylon:			
Rural Cingalese	296	14·39	1·73
Colombo city schools (various eastern races)	844	12·84	1·24
Southern England ..	2,590	13·49	1·19

onset of menstruation may be calculated by the statistical technique of probit analysis. The results, together with those of Ellis (1950), are summarized in the Table.

The menarche occurs relatively late in the hot dry climate of the Northern Nigerian savannah (14.14 years, with a remarkably low standard deviation), on the more temperate Plateau (14.50 years), and in Central India (14.65 years), where high temperature and high humidity are combined. The observations in Ceylon are of special interest. The onset in the rural group of Cingalese children (14.39 years) approximates to that in Nigeria and Central India, but the urban children in Colombo show an early onset of 12.84 years. This city group is racially mixed, and includes Cingalese Burghers of Dutch origin and Tamils from South India, each with their own social environment. It is unfortunate that our records do not permit a subdivision of this group into more homogeneous racial units.

The groups of children studied differ in food habits, nutritional status, and social environment, as well as in climate and race. Without much more extensive observations it is not possible to assess the relative importance of these differences in influencing the age of the menarche. It is, however, clear that in tropical countries the onset of menstruation, compared with that for English children, may be either early or late, and that in these latitudes it is not determined solely by the climate.

We acknowledge the help received from Dr. Claire Thomson, of the S.P.G. Mission in Central India, and from Dr. Anne Gall in Northern Nigerian schools.

DAGMAR C. WILSON, M.D., M.R.C.P., F.R.C.O.G., D.P.H.
IAN SUTHERLAND, M.A., D.Phil.
Laboratory of Human Nutrition, University of Oxford; Medical Research Council's Statistical Research Unit, London.

REFERENCES
Ellis, R. W. B. (1950). *British Medical Journal*, 1, 85.
Wilson, D. C., and Sutherland, I. (1950a). Ibid., 1, 1267.
—— —— (1950b). Ibid., 2, 862.

A *Directory and Catalogue of Collections of Micro-organisms Maintained in Australia* is now available from the Commonwealth Scientific and Industrial Research Organization, Melbourne. It has been prepared, in common with other Commonwealth directories, on the recommendation of the British Commonwealth Specialist Conference on Culture Collections of Micro-organisms held in London in 1947. The Australian directory lists 42 institutions where collections are maintained. In each case the address of the institution, the name of the doctor, and the types of cultures maintained and how they are distributed are given. In addition there is an alphabetical list of species which shows where each species may be obtained in Australia.

Reviews

TRENDS OF LIFE

Trends of Life. By F. Wood Jones, F.R.S. (Pp. 191. 10s. 6d.) London: Edward Arnold. 1953.

In this short book of 190 pages Professor Wood Jones summarizes the ideas at which he has arrived after a whole lifetime's study of living things. He declares himself unashamedly unorthodox. He believes that "the distinction of living matter is its power of self-maintenance which is manifested in activities that are characteristically directive." In his opinion this basic quality of life has been concealed by the developments in biology which were inspired by Darwin's theory of natural selection as the main cause of evolution, and he suggests that the essence of the matter is also overlooked in most modern laboratory experimentation.

In support of his views Professor Wood Jones mentions many examples of adaptations by animals to the special circumstances of their lives, and of forms of behaviour which permit them to survive and multiply. In many cases I do not find at all convincing his argument that such phenomena cannot be easily explained by natural selection. Nevertheless, there is little doubt that the orthodox and simple form of the theory of natural selection is not altogether adequate to explain all the facts that one can discover in nature. It is salutary for experimental biologists to be challenged from time to time by those who have made a wide study of the forms and activities of living things, but this is perhaps more likely to lead to a development of our modern theories than to the supersession of them which Professor Wood Jones seems to call for. But he has rendered a service of great value to science by showing afresh the whole range of the problems which have to be faced.

The book ends with a consideration of man and his future in the light of the point of view which Professor Wood Jones has developed about the evolutionary process in general. He is extremely pessimistic. Man, he says, has become a barbarian "everywhere engaged upon a campaign for the wholesale obliteration of life," and he regards it as inevitable that the total food yield of the earth will eventually diminish. The state of the world is certainly not such as to inspire one with great confidence, and prophecies of woe are perhaps not out of place: but they have been survived before.

C. H. WADDINGTON.

DIFFERENTIAL DIAGNOSIS

Clinical Investigation: A Manual for Practitioners and Students. By E. H. Stokes, M.D., Ch.M.(Sydney), F.R.A.C.P. Foreword by G. E. Beaumont, D.M., F.R.C.P., D.P.H. (Pp. 628; 344 figures and 6 coloured photos. £5 5s.) London and Sydney: Angus and Robertson. 1953.

This book is unusual in that it combines a careful and detailed description of clinical methods with consideration of the significance of symptoms and regional physical signs. It is much more, therefore, than a primer for medical students, and may be accepted as a textbook of differential diagnosis with special emphasis on the detection and understanding of physical signs. The author has performed his task with conspicuous success.

First, he describes the art of case recording, and then follow sections on the general appearance of the patient and examination of the main bodily systems. The more important biochemical investigations are referred to in the appropriate sections, and in an appendix the author sets out the normal values for various blood and cerebrospinal-fluid constituents—a most helpful addition which might well be adopted by all authors of textbooks of medicine.

In considering the position of the apex of the heart by palpation the value of sitting the patient up should be mentioned. Failure to do this to the obese has brought

many an examination candidate to disaster. The list of causes of prolonged pyrexia might be omitted, for it is of no help. Our old friend the caput medusae rears its serpiginous head, yet how very rare it is compared with large veins scorning the umbilicus and running roughly parallel to one another. That the Schindler gastroscope fails to reveal the cardia is largely true, but it is many years now since the more effective Hermon Taylor instrument first allowed us to view this area with ease. The book is profusely illustrated with photographs, most of which are technically excellent and well chosen. The coloured photographs are less happily reproduced, with the exception of that of myxoedema, which is life-like. The book is so good that it can bear these few criticisms, for in its class it is outstanding and of great value both for routine reading and for frequent reference.

A. H. DOUTHWAITE.

HORMONES AND HEART DISEASE

Hormonal and Neurogenic Cardiovascular Disorders: Endocrine and Neuro-endocrine Factors in Pathogenesis and Treatment. By Professor Wilhelm Raab, M.D., F.A.C.P., F.A.C.C., F.C.C.P. (Pp. 722; 82 illustrations. £5 14s.) London: Baillière, Tindall and Cox. 1953.

Current conceptions of mechanisms in cardiovascular disease do not go very deeply into fundamentals. We are inclined to accept angina pectoris as ischaemia of the cardiac muscle resulting from coronary sclerosis. Dr. Raab points out, with extensive quotations from the literature (3,726 references), that adrenal medullary secretions cause waste of oxygen by the heart and also degenerative lesions of the vascular walls. Lack of thyroid hormone is said to protect the heart from these effects but to favour the development of atherosclerosis, while excess of thyroid hormone potentiates the action of adrenaline. These hormonal influences, Dr. Raab thinks, are of vital importance in the production of cardiovascular disease. He admits frankly that some of his views are highly speculative. None the less, he brings a wealth of knowledge to bear on his problems, and everyone interested in cardiovascular disease is likely to find his ideas of great interest. But the book should be read critically, for it is full of thought-provoking notions which are not yet proved. Its value may lie in suggesting starting-points for further research.

J. MCMICHAEL.

MALE STERILITY

La Sterilità nel Maschio: Fisiopatologia degli Organi della Reproduzione. Diagnostica e Terapia dell'Infertilità Maschile. By Guglielmo Longo. (Pp. 520; illustrated. 4,000 lire.) Salerno: Diffusion Scientifique Internationale. 1953.

Physiology of reproduction has long been a domain in which Italian men of science have excelled and to which they have contributed many observations as well as some of the greatest discoveries. One has only to recall the brilliant researches of Malpighi and Spallanzani to be reminded of the wealth of fundamental facts which modern physiology owes to the Italian pioneers of the seventeenth and eighteenth centuries. Their followers, men such as Mantegazza and Sertoli, have maintained the fine tradition, and in the present century several physiology schools in Italy can point with pride to important and original work on manifold aspects of fertility and sterility.

This monograph by Dr. Longo, of the Salerno School of Obstetrics, contains not only much information of historical interest but is a valuable source of information on the most modern developments in physiology and clinical aspects of male fertility. It covers an unusually wide range of subjects, which are described and discussed in four separate parts. Part I is mainly on the anatomy and physiology of male reproductive organs, but includes also large sections devoted to the physiological mechanisms of sperm formation, ejaculation, and transport in the female tract. Part II is an attempt to classify on a physiological basis the various deficiencies and dysfunctions which underlie infertility in men. Part III deals specifically with laboratory methods used in semen analysis and in the diagnosis of the various forms of male subfertility or sterility. Part IV, of particular importance to practising physicians, is a detailed discourse on the prophylaxis and therapy of male subfertility.

The book is a useful source of reference for clinicians, and takes fully into account recent advances in knowledge gained, particularly during the last decade, on the physiology, pathology, and biochemistry of semen and the human male reproductive tract in general.

T. MANN.

CHILD PSYCHIATRY

Psycho-Analysis and Child Psychiatry. By Edward Glover, M.D. (Pp. 42. 6s.) London: Imago Publishing Co. 1953.

This short statement is of value to those who are immersed in child psychiatry, who enjoy new ideas of all kinds, and who nevertheless wish their theoretical contributions to gain by being related to the Freudian basis which has made their work possible. The author gives a clear presentation of the way Freud's always developing theory led to reconstructions of childhood and infancy, and of how work with children necessitated a recognition of the inadequacy of theory derived from analysis of neurotic adults.

Unfortunately Glover's dislike of Klein's ideas continues to colour his work, and indeed this otherwise excellent booklet is marred by a pointless acerbity, directed apparently against anyone who practises psycho-analysis. His references are all to his own works or to those just outside psychoanalysis proper. An editor who had cut out all the tendentiousness would, by a dozen blue-pencillings, have transformed this little work into a simple and valuable scientific contribution. But this has not happened, and Glover seems now to be out of touch with the developments that have taken place in those who were once his pupils and colleagues.

As an example on the positive side, Glover's classification is as follows: (*a*) disturbances of function (inhibitions and exaggerations); (*b*) disturbances of development (regressions, fixations, and precocious advances); and (*c*) symptom formations (psychoneurotic, pre-psychotic, and psychotic). This scheme, with the addition of a plan for various types of external factor, can be made to work, and its simplicity is not artificial. There is much else that those who have actual experience of the analysis of children and of the practice of child psychiatry may learn from this booklet by one who, although not in charge of children, has had a wide experience with older patients, and who can think.

D. W. WINNICOTT.

INTRODUCTION TO OBSTETRICS

The Anatomy and Physiology of Obstetrics: A Short Textbook for Students and Midwives. By C. W. F. Burnett, M.D., F.R.C.S., F.R.C.O.G. With illustrations by Susan Robinson, M.M.A.A. (Pp. 168; 81 figures. 15s.) London: Faber and Faber. 1953.

The purist might quarrel with the title of this book, but it serves to indicate that the range of its subject-matter is the anatomy and physiology of those parts of the mother and of the foetus which are of immediate concern to anyone practising obstetrics. The account is concise and simple, and is designed primarily for pupil midwives, but also with the idea of assisting medical students and candidates for the midwife teacher's diploma. A few sections are noted as being too detailed and advanced for the pupil midwife. The arrangement mostly takes the form of numbered paragraphs, and, although these are logical and easy to follow, it is inevitable that they sometimes amount to a sequence of factual statements, difficult for the uninitiated to digest. It will undoubtedly be useful to the type of reader for whom it is intended, but perhaps more as a supplement to lectures than as a textbook.

T. N. A. JEFFCOATE.

BRITISH MEDICAL JOURNAL
LONDON
SATURDAY SEPTEMBER 12 1953

RETROLENTAL FIBROPLASIA

It is not often that a "new" disease appears as an entity apparently without pathological relatives, and when its effect is to cause incurable bilateral blindness in newly born children its medical interest becomes overshadowed by the sense of urgency to alleviate a social and economic catastrophe. It is quite probable that retrolental fibroplasia has escaped special notice or been misinterpreted until recently because of its rarity and sporadic occurrence. But since the initial description by Terry[1] in 1942 of the sudden appearance of numerous cases in Boston it has been recognized—occurring sometimes sporadically, sometimes in minor epidemic form—in many countries of the world, particularly in the United States and Great Britain. Typically it affects prematurely born children, especially those whose birth weight is in the region of 3 lb. (1.3 kg.)—the great majority of the affected infants having been reared in hospitals. Two decades ago the homes for blind children in this country had a high proportion of the partially blind victims of venereal ocular infection; one decade ago these patients were largely eliminated owing to the use of antibiotics; to-day their place is being taken by totally blind children afflicted by retrolental fibroplasia.

The pathology of the condition seems clear. The initial change is angioblastic in nature, with proliferation of endothelial cells and then of vessels from the retinal circulation into the vitreous; this is followed by fibroblastic changes, until eventually the new-formed fibrous tissue detaches the retina and stretches in a solid sheet behind the lens. Despite a large amount of research and a larger amount of speculation, the cause of these changes remains unknown. A variety of theories have been advanced. Terry's original suggestion was that the aetiological factor was precocious exposure to light, but others have put forward as possible causes embryological anomalies associated particularly with the hyaloid system of vessels, lack of vitamins, metabolic disturbances in the premature infant, and an infection (presumably viral). A number of investigators have incriminated oxygen, explaining the recent prevalence of the disease by the increasing use of oxygenation in the treatment of premature infants in modern clinics. The disease occurs essentially in units for premature infants in hospitals, and since some institutions have reported its initial appearance or increased incidence when the concentration of oxygen in the tents has been high, and others when it has been lowered, speculation has been divided on whether hyperoxia or anoxia is the causal factor.

In these circumstances the Medical Research Council set up a committee about a year ago, under the chairmanship of Sir Stewart Duke-Elder, to correlate investigation into the cause of the disease by ophthalmologists, paediatricians, gynaecologists, and the Ministry of Health. Under this stimulus the results of some important research on the role of oxygen in the genesis of retrolental fibroplasia have now appeared in the current issue of the *British Journal of Ophthalmology*.[2] The work was done in the Institute of Ophthalmology, London, and it would seem probable that the first hopeful approach to the experimental production of the condition has been achieved. The kitten was chosen as the experimental animal, since at birth the stage of development of its eye corresponds roughly to that of the premature infants most prone to develop the disease. It was found that if litters of kittens were kept continuously in 70 to 80% oxygen for periods of several days after birth the developing retinal vessels became completely obliterated, leaving only a few remnants at the optic disk, while the fully developed hyaloid system was unaffected. The extent of the obliteration is directly proportional to the degree of immaturity of the retinal vascularization, the duration of exposure to oxygen, and to the concentration of oxygen. When the kittens were returned to ordinary air the vessels grew again from the disk, forming not a well-ordered network but a luxurious irregular system, preceded by haemorrhages and showing numerous corkscrew proliferations which extended as glomerular tufts into the vitreous—exactly as in retrolental fibroplasia. A somewhat similar although less profuse neovascularization occurs if the young kittens are kept in low concentrations of oxygen (10–15%). It is thus possible but more difficult to produce the condition by simple hypoxia alone: the ideal conditions are attained only in the state of relative anoxia after obliteration of the normal vascular supply by hyperoxia.

The experiments described are only a preliminary series and they have been published at this early stage for obvious reasons. If the results are confirmed interesting general questions about the stimulus for neovascularization will be raised, and if the experi-

[1] *Amer. J. Ophthal.*, 1942, **25**, 203 and 1409.
[2] Ashton, N., Ward, B., and Serpell, G., *Brit. J. Ophthal.*, 1953, **37**, 513.

ments are extended it would seem likely that they will offer a basis for bringing together the divergent opinions held at present on the cause of retrolental fibroplasia. It does not necessarily follow that abnormal vascular proliferations in the premature baby occur exactly as in the newly born kitten, nor that the whole of the aetiology of the disease is explained by this one factor; but it seems reasonable to suggest that these preliminary results may explain the recent high incidence of the disease and its occurrence in apparent epidemics in clinics; while the occasional occurrence of retrolental fibroplasia in infants who have not been exposed to abnormal concentrations of oxygen may conceivably be associated with prolonged anoxia from maternal or foetal causes. Fortunately the obvious practical application of these results to the rearing of premature infants does not appear too difficult, and it may be that retrolental fibroplasia, in so far as it is a common disease, will be found to disappear as dramatically as it appeared.

RESINS AND CARDIAC OEDEMA

Sodium retention is an important feature of cardiac oedema, and the treatment of congestive failure should include efforts to prevent it. These are in addition to measures intended directly to improve the function of the heart. The intake of sodium may be limited by means of low-sodium diets and the output increased by means of mercurial diuretics. But a diet sufficiently low in sodium is sometimes difficult for the dietitian to produce and even harder for the patient to take. As a consequence of the suggestion by Dock[1] that certain resins might be used to withdraw sodium from the gut, interest has been directed to these new preparations. Cation-exchange resins are substances of high molecular weight. They are formed by the condensation of molecules of either sulphonic or carboxylic acids containing many free valency bonds. These are available to combine with cations, including hydrogen ions. Resins exchange cations according to the laws of mass action, the affinity for divalent being greater than for monovalent ions. Physically they are hard, gritty, insoluble powders, and when given by mouth in the hydrogen or ammonium form they liberate these ions in exchange for sodium, which is excreted in the faeces in combination with the resin. Thus, while the hydrogen or ammonium ions are absorbed in combination with acid, the absorption of dietary sodium is reduced. The capacity for ion uptake of such resins is greater *in vitro* than in the gut, and 1 g. of resin seldom combines with more than 0.5 to 1 mEq of sodium in oedematous subjects.[2 3] Generally the resins merely prevent absorption of sodium, depletion of the body's sodium being achieved by increased renal elimination.[4] But recently Duncan[5] has found that faecal sodium excretion may greatly exceed dietary intake during resin therapy, and Weston *et al.*[6] obtained negative sodium balances by removal of sodium from the gut in oedematous patients.

Patients may become resistant to mercurial diuretics (which cause a chloride rather than a sodium diuresis) owing to the development of a hypochloraemic alkalosis. Resins remove sodium rather than chloride, and those in the hydrogen cycle produce an acidosis, thus redressing the balance and restoring the response to mercurials. But they have certain disadvantages and even dangers. Pharyngeal and gastro-intestinal irritation may occur. Resins are unpalatable, sometimes nauseating, and must be taken in large amounts (50–100 g. a day). They remove potassium and calcium as well as sodium, and serious hypokalaemia and hypocalcaemia have been reported after prolonged treatment. The risks of hypokalaemia can be reduced by saturating the resin with potassium, but then care must be taken to prevent accumulation of this cation in patients with renal insufficiency. Greenman *et al.*[3] used a carboxylic cation exchange resin (80% in the hydrogen and 20% in the potassium cycle) as a supplement to the usual therapy in patients with congestive cardiac failure for periods of up to fifteen months. They noted no dangerous electrolyte deficiencies up to six months, but subsequently hyponatraemia, hypocalcaemia, and hypokalaemia developed. Unfortunately it was not possible to increase the sodium intake significantly without reducing the efficiency of the resin, while substitution of the potassium for part of the hydrogen form of the resin reduced its sodium-binding power from 0.75 mEq to 0.28 mEq of sodium per gramme of resin.

Ion exchange resins which have been used in Britain for treating congestive heart failure are "zeo-karb 225," a sulphonated polystyrene resin, and "resodec," a carboxylic resin in the ammonium-potassium cycle. Barker *et al.*[2] reported satisfactory results with the former, but noted a gradual decline in the response of two patients with congestive cardiac failure who were treated for five weeks with 100 g. daily. They attributed the falling response to reduction in the sodium content of the gut. Peel and Semple[7] treated ten patients with refractory or recurrent congestive cardiac failure with 45 g. of resodec daily. Nine of their patients were receiving an

1 Dock, W., *Trans. Ass. Amer. Phys.*, 1946, **59**, 282.
2 Barker, R. A., *et al.*, *Lancet*, 1951, **2**, 758.
3 Greenman, L., *et al.*, *Amer. J. Med.*, 1953, **14**, 391.
4 Mateer, F. M., *et al.*, *J. clin. Invest.*, 1951, **30**, 1018.
5 Duncan, L. E., *Amer. J. Med.*, 1953, **14**, 425.
6 Weston, R. E., *et al.*, ibid., 1953, **14**, 404.
7 Peel, A. A. F., and Semple, T., *Brit. Heart J.*, 1953, **15**, 350.

ordinary ward diet. Oedema was abolished in four cases, lessened in seven, and unchanged in three. Slightly better results were obtained when the resin was given in conjunction with a low-sodium diet. Acidosis due to hyperchloraemia occurred on three occasions, hyperkalaemia twice, and hypokalaemia twice. When resodec was used in addition to a low-sodium diet, the best results were obtained with repeated short courses.

The combination of a low-sodium diet, mercurial diuretics, and digitalis is a satisfactory regimen for most patients with congestive cardiac failure. Cation exchange resins in their present form will be needed only in the minority of cases. They should be reserved for patients who become refractory to mercurial diuretics as a result of hypochloraemia, for those who develop sensitivity reactions to mercurials, and for those who cannot be sufficiently freed of oedema by the usual methods. Treatment with resins might also be justified in patients who cannot tolerate a diet sufficiently low in sodium to control oedema. A resin in the potassium-ammonium cycle should be administered, preferably in conjunction with a low-sodium diet; short periods of resin therapy could alternate with the administration of mercurial diuretics. Special care should be exercised to prevent hyperkalaemia in patients with primary renal insufficiency. Since accurate biochemical control is essential, patients should be treated initially in hospital, and, in view of the complications of excessive sodium depletion—including acidosis, hypocalcaemia, and hypokalaemia—which may develop after a few months' treatment, it is doubtful at present whether there is a place for prolonged maintenance resin therapy in domiciliary or out-patient hospital practice. The ideal resin would be one which would permit a more liberal diet, effectively remove sodium from the body in addition to preventing its absorption, and yet not deplete the body of other essential ions. It is not yet available.

INFANT DEATHS

Few indications of medical progress give more grounds for satisfaction than the continued improvement in stillbirth and infant mortality rates. A hundred years ago, of infants who reached viable age (28 weeks' gestation) in England and Wales, at least one in five was stillborn or died before the first birthday; in 1952 the corresponding proportion was one in twenty. Moreover, we have not seen the fulfilment of the pessimistic predictions of Karl Pearson and others: they suggested that the survival of infants who in sterner days would have died at an early age might eventually be reflected in reduced expectation of life.

But will the trend continue? How far can the stillbirth and infant mortality rates be expected to fall below their recent low levels of 23 and 28 respectively in England and Wales in 1952? It would be possible to give a more confident answer to these questions if we had more precise information about cause of death. Much is known about deaths—mainly from infectious disease—in the later months of the first year, and about the means by which they have been prevented. Moreover, the sharp differences in infant mortality noted by Woolf[1] in association with family size are largely attributable to infection,[2] and give reason for believing that the possibilities of the traditional methods of prevention are by no means exhausted. It is with stillbirths and early neonatal deaths that more serious difficulty appears, for it is not certain to which measures recent improvement is attributable, and knowledge of cause of death is still far from complete.

It is to this problem that Baird, Thomson, and Duncan[3] turned their attention in an investigation of "obstetric deaths," under which term they include stillbirths and deaths in the first week of life. They observed that in Aberdeen the stillbirth rate fell sharply between 1942 and 1945, and the decrease was noted in deaths from all causes except foetal deformity. The considerable reduction in the incidence of stillbirths and first-week deaths due to prematurity and other ill-defined causes is attributed by these authors to improved maternal health and nutrition.

An analysis of the so-called "hard core" of stillbirths and infant deaths, of which the largest and best-defined group are the congenital malformations, must precede any assessment of the possibility of reducing mortality in early life. Until recently investigations of the cases due to malformation might have been regarded as of interest mainly to the geneticist; but the fact that their incidence has remained more or less constant, while that of most other causes of death has fallen sharply, has brought them into prominence. In the white population of New Zealand, for example, they recently accounted for about one-fifth of all deaths under 1 year, and Scottish data indicate that about 1% of all foetuses alive in the uterus at the 28th week of pregnancy are dead because of congenital malformations before the first birthday.[4]

Happily there is reason to believe that at least some of the malformations are not the hopeless genetic problems they were once thought to be. The association with rubella is now well established, and, although shown to be relevant to only a limited group of abnormalities, is none the less important as perhaps the firmest evidence of environmental influence in the aetiology. Another promising line of inquiry is the production of malformations in experimental animals, of which an interesting example is provided by the work of Warkany and his colleagues[5] on dietary deficiencies. More recently the association of incidence with maternal age or birth order has also been used as a means of establishing environmental influence. This method, employed by Penrose[6] in the investigation of mongolism, has been

1 Woolf, B., *Brit. J. soc. Med.*, 1947, **1**, 73.
2 Gibson, J. R., and McKeown, T., ibid., 1952, **6**, 183.
3 Baird, D., *et al.*, *J. Obstet. Gynaec. Brit. Emp.*, 1953, **60**, 17.
4 Record, R. G., and McKeown, T., *Brit. J. soc. Med.*, 1949, **3**, 183.
5 Warkany, J., *Obstet. gynec. Surv.*, 1948, **3**, 693.
6 Penrose, L. S., *Ann. Eugen. Lond.*, 1934, **6**, 108.
7 McKeown, T., *et al.*, *Arch. Dis. Childh.*, 1952, **27**, 386.
8 MacMahon, B., *Brit. J. soc. Med.*, 1952, **6**, 178.

exploited with great skill at Birmingham in a number of other abnormalities. The evidence suggests that the environment contributes to the causation of malformations of the central nervous system,[4] infantile pyloric stenosis,[7] and possibly patent ductus arteriosus.[8]

The conspicuous reduction in early mortality during the last fifty years was due mainly to success in controlling the post-natal environment. If this trend is to continue much further, it will be necessary to prevent some of the deaths whose cause is determined before or during birth. Recent work may not yet have taken us very far towards the goal of prevention, but by establishing the importance of the pre-natal environment in aetiology it has provided grounds for the belief that it may eventually be possible to bring some at least of the major malformations under control.

GENES AND ENZYMES

The generalization "One gene—one enzyme" is an attractive one, and last year Sir Macfarlane Burnet suggested[1] that it might, if finally established, "represent one of those great simplifying concepts like the idea of evolution by natural selection or the quantum theory." Medical men bewildered by the headlong advances of genetics may be uncertain just what is implied by this new candidate for a place among the supreme scientific ideas. But in fact its origin may be traced back to the essentially medical work of A. E. Garrod in the early years of the century. He showed[2] that certain abnormal conditions which are inherited in a relatively simple Mendelian fashion (for example, alkaptonuria in man) are probably due to the absence of an enzyme which is present in normal individuals. From this has sprung the hypothesis that Mendelian genes operate by controlling the specificity (and thus the effectiveness) of cellular enzymes. If an animal is homozygous for a mutant gene, then all its supplies of a certain enzyme will be of altered efficiency, and some synthesis usually performed by this enzyme during the animal's development will take place at an abnormal rate, or more probably not at all.

The grounds for this belief have been enormously widened in recent years by studies of such micro-organisms as fungi, yeasts, and bacteria. Normal individuals of most of these groups can grow on extremely simple media. By applying treatments such as x rays or mustard gases known to cause mutants, abnormal races can be produced. Breeding tests show the abnormality to be dependent on the presence of single gene mutants. When the organisms are tested for their nutritive requirements, it is nearly always found that they cannot grow on the basic minimum medium which suffices for the normal individual, but require the addition of some single supplementary substance. The implication is that the mutant gene has altered and inactivated the enzyme by which this substance is usually produced.

This type of experiment has proved to be exceedingly informative in analysing the sequences of metabolic changes in such lowly forms, since mutants can be isolated in which the chain of metabolism has been broken at its first, or at its second, or at some subsequent link. But the "One gene—one enzyme" idea still remains in the realm of hypothesis rather than fact. One reason is that only in very few cases is the condition of the enzymes in the mutant race known; the fact is that a certain substance is not produced, and to attribute this to an absence or alteration of an enzyme is the simplest, but not the only, hypothesis. Moreover, geneticists are nowadays by no means confident of what they mean by "one gene." It is possible that the elements of physiological activity are short segments of chromosomes which are not quite sharply bounded against each other, but shade off through a transition zone from one to the next. Finally, the experiments in which the "One gene—one enzyme" idea finds its main support are on micro-organisms, where there is no differentiation of the body into various tissues. Even if a given gene affects only one enzyme in, say, the pancreas, may it perhaps affect quite a different one in the liver? At first sight this seems to happen sometimes, but there is no convincing evidence one way or the other.

1 *Lancet*, 1953, **1**, 103.
2 *Inborn Errors of Metabolism*. London: Henry Frowde. 1923.

LEAD IN LOLLIES

Despite the fears so often expressed about the possible toxicity of small quantities of the many new and complex chemical substances being brought into man's immediate environment, the older and chemically simpler poisons continue to offer a threat to health and well-being. Of these lead may perhaps be described as a hardy annual. Not long ago it was the danger from the use of lead nipple shields that aroused considerable discussion. Now attention has been drawn to another possible danger arising from the sucking habits of older children. Everyone is familiar with iced lollies, of varied and often hideous hues, and with the sticks upon which they are frozen, for these litter the ground in increasing profusion. Semple[1] has recently reported that these fashionable confections may contain up to 11 parts per million (p.p.m.) of lead. In addition copper, tin, and zinc may be found in amounts up to 11, 70, and 5 p.p.m. respectively. A careful analysis of the ingredients and mode of preparation showed that the metals came from the moulds in which the water and coloured syrups are frozen to make the lollies. The moulds may be made of poor quality tin plate or be soldered with lead solder. Apparently plastic moulds are not popular because they increase the time needed to complete the freezing of their contents. Aluminium moulds might overcome this difficulty and avoid risks from lead contamination.

Copper in the amounts found is unlikely to be harmful; tin is present in many preserved foods and permitted in concentrations up to 250 p.p.m.; and zinc is not known to be harmful in these concentrations. Whether the risks of chronic poisoning from lead in quantities as small as this are serious is difficult to assess, for opinions differ widely. It has been stated that there are 10,000 references to the biological action of lead published since 1616, but "in no instance has it been definitely established on a single species of animals just how little (lead) will cause chronic toxicity when ingested over long periods of time."[2] The absence of such informa-

1 *Med. Offr.* 1953, **90**, 74.
2 Calvery, H. O., Lang, E. P., and Morris, H. J., *J. Pharmacol.*, 1938, **64**, 364.
3 Monier-Williams, G. W., *Trace Elements in Food*, 1949. London.

tion has not inhibited medical writers from suggesting what would constitute a dangerous daily dose for man. Of 40 authorities who have ventured an opinion, 36 suggest a figure of less than 0.1 mg. daily.[2] However, a safe limit for domestic water is considered to be 0.3 p.p.m., which would mean a daily intake of 0.5 mg. if three pints of water were drunk each day.[3] Though there may be disagreement about figures among the experts, few would dispute the view that lead is an undesirable ingredient of any food or drink. Its access to iced lollies can be prevented by ensuring that these colourful delights are prepared in suitable containers, and it would seem reasonable to make it illegal to sell lollies containing lead in a higher concentration than that found in the local drinking-water.

SANITARY INSPECTORS

For the past two years a working party appointed by the Minister of Health has been looking into the recruitment, training, and qualification of sanitary inspectors—a group of men whose work in the preventive field has not always had the appreciation it deserved. The recently published report[1] of the working party gives full weight to the improvement in the status, education, and responsibility of sanitary inspectors since their office was first established about one hundred years ago. In those days they were often called inspectors of nuisances, but the scope of their work has greatly increased since then, and the popular notion that the work of sanitary inspectors is mainly concerned with drains has largely been dispelled. Even so, the working party thinks that the term "sanitary inspector" gives a false impression of the present nature of the job, and recommends the new title of "public health inspector."

In seeing that legal requirements are complied with sanitary inspectors now rely on advice, persuasion, and education, and use the courts as a last resort. It is not surprising, therefore, that there have been changes in the sources of recruitment and that higher standards of education are now required. While the duties of sanitary inspectors are spread over a wide field, some of which is outside the province of public health, their time is now principally taken up with housing and food inspection. As regards the inspection of meat and other foods, the working party considers that the existing standard of training in the present basic course should be raised to a level not lower than that now required for the supplementary certificate at present taken by practically all sanitary inspectors after their qualifying examination. A recommendation is also made that more attention should be given in the basic examination to smoke abatement, insect pest control, local government administration, and public health in general. The working party has also scrutinized the composition of the present examination board—a compromise product of early controversies. The report recommends the appointment of a new authority to be responsible for examinations and certificates for the office of sanitary inspector. The composition of the proposed board would represent an appropriate balance of the interests concerned with the sanitary inspectors' duties, and its members would include sanitary inspectors, medical officers of health, and representatives of employing authorities.

In reviewing the existing arrangements for the practical training of students, the working party found wide variations and as a consequence has recommended that such training should be undertaken only with local authorities approved for that purpose. It is also urged that ultimately the sole avenue of entry should be by way of paid pupillage. There are several reasons for a recent falling off in recruitment, but the working party considers that the adequacy of the salary now paid to sanitary inspectors merits the attention of the employing authorities. Adoption of the report's recommendations should lead to a comprehensive scheme of recruitment, training, and qualification which would ensure that local authorities have sanitary inspectors fully capable of discharging their increasing responsibilities.

[1] *Report of the Working Party on the Recruitment, Training and Qualification of Sanitary Inspectors*, 1953, H.M.S.O., London.

INFECTIVE HEPATITIS IN DOCTORS

Recent statistical studies in Sweden and Denmark have shown that doctors seem to be more liable to suffer from hepatitis than the rest of the community. Strömbeck,[1] writing from Stockholm, states that since infectious jaundice or hepatitis was included among the notifiable diseases in Sweden in 1931 the notified cases have shown an enormous rise. During the seven-year period 1931–7 the annual total of these notifications was about 1,300. During the period 1943–6 there were some 7,000 cases notified every year, and in 1948 there were 11,736 such notifications. Strömbeck addressed a questionary to 4,030 doctors in Sweden, classifying them into those in general practice, those in hospital practice not concerned with surgery, and surgeons in hospital practice. He found that the hepatitis rate was higher among doctors in hospital than among doctors in general practice, and higher among the operating hospital doctors than among the hospital doctors who did not operate. His conclusion was that Swedish doctors suffer from a higher hepatitis rate than the community as a whole, and he suggested that it would be desirable to compare the morbidity rate in different occupations. Such a comparative study was undertaken by Madsen,[2] who addressed inquiries to a total of 10,000 persons in Denmark. They were asked to state if they had suffered from acute hepatitis before the age of 18 years or after this age. Among them were 4,700 doctors, 2,000 lawyers, 2,190 employees of three large industrial concerns, and 1,179 hospital nurses. Above the age of 18 the hepatitis rate was 10.4% for doctors, 7% for lawyers, 6.8% for nurses, and only 3.9% for industrial workers and employees. As doctors are supposed to be more exposed to infections, their high hepatitis rate may not be surprising, but, as Madsen points out, it is curious that hospital nurses should have such a comparatively low rate, one that is slightly below that of lawyers, who are presumably much less in contact with infectious material than are nurses.

[1] *Svenska LäkT.*, 1952, **49**, 265.
[2] *Ugeskr. Læg.*, 1952, **114**, 951

FIRST WORLD CONFERENCE ON MEDICAL EDUCATION

CLOSING PLENARY SESSIONS

This report concludes the account of the Conference. The inaugural session, the proceedings of the four Sections, and the concluding proceedings were reported in our issues of August 29 and September 5.

The Conference closed with two plenary sessions held at Friends House, London, on Friday afternoon, August 28, and Saturday morning, August 29. The first was held under the chairmanship of Sir LIONEL WHITBY, and the second under that of Professor W. MELVILLE ARNOTT. The speeches in which the Vice-Presidents of the Conference and the rapporteurs summed up the work of the four Sections are reported in full below.

SECTION A: REQUIREMENTS FOR ENTRY INTO MEDICAL SCHOOLS

Dr. VICTOR J. JOHNSON (Mayo Foundation for Education and Research, Rochester, Minnesota), who had been in the chair of Section A, spoke as follows:

Last evening the Section rapporteur and I tried to distil from a multiplicity of manuscripts, many memoranda, and our own recollections the essence and spirit of our meeting. We felt very sorry for ourselves, because we knew that many of you were otherwise engaged with distillates and spirits. Obviously only general impressions can be recorded. A major impression at the opening plenary session was Sir Richard Livingstone's definition of an educated man as one who knows and values what is first-rate.[1] I recognize and acknowledge that this Conference has been first-rate. I had nothing at all to do with the conception and planning of it, and I must confess that I had a measure of scepticism regarding its outcome. Those who did conceive and plan it were wiser than I, and I repeat that I believe the Conference was first-rate. Perhaps to appreciate its worth fully we must await publication of the *Proceedings*, which will be an encyclopaedia of factual information and considered opinion about medical education in all quarters of the globe.

An important segment of the thinking in our Section was dedicated to the proposition, supported unanimously, that a physician first of all must be an educated man or woman. He must know and appreciate what of the handiwork of man is first-rate in the humanities and social and natural sciences. Moreover, he must not only secure but continue to seek after the first-rate—the good, the beautiful, and the true—long after teaching and classes and assignments and examinations have receded into the past. Let us not be impatient to encompass all we have to learn into the period of formal education. Let us seek to canalize a living, insistent appetite for learning, always feeding but never to be sated.

The papers in our Section were studded with many erudite quotations. One of the most cogent for a question of this kind pertained to the dean or educator seeking at his own school to implement some of the wise educational proposals advanced at this Conference. The aphorism reads, "It is easier to move a graveyard than to change the curriculum."

Problems of Selection

Although everyone flashed the green light of "Go ahead" to a liberal education, current practice for selecting medical students displayed a spectrum from red to violet, with a complementary colour at each wave band. Vyshinsky would have compared this session to a meeting of the Security Council. The confusion as regards admission practice was even reflected in a confusion in the proceedings of the Section. At one point a discusser emphatically disagreed with an opening speaker, and, amazingly, the speaker joined the critic in attacking the paper he himself had just read. It turned out that the paper was written by somebody else entirely, someone who was not even present at the Conference.

Just such a puzzling situation characterized the problem of selecting the medical student. Not only was there warm disagreement regarding technique for selection, but there was a question whether there should be any selection at all. Some schools in some countries apparently admit all who have the minimum requirements. Most of these fall out of the train or are pushed off at each station. At the opposite end of the spectrum, some schools in some countries devote tremendous effort to admitting only those students whom they judge competent to become physicians. On the one hand, there may be reasons for some schools admitting large numbers of students many of whom are expected to fail; on the other hand, it is plain that other schools consider it worth while to develop and refine the technique for admission. I venture to suggest that schools with low admission requirements consider ways and means of admitting approximately as many students as they anticipate graduating. I say they might well consider ways and means—that is a suggestion, not a resolution.

The pros and cons of many techniques for selection were discussed at length. As an example, this morning the efficacy of an important selection technique, the intelligence test, was effectively and dramatically challenged on the basis, not of opinion, but of experimental study. Statistical analysis of the results revealed a complete lack of correlation between intelligence test scores and numerical results at school examinations. However, it was possible to select a critical scoring and predict with considerable assurance that those falling below the selected point were almost certain to fail in the medical school.

During this week my most pleasant and profitable association has been with my colleague, Dr. Raymond Whitehead, the rapporteur. From him you will hear presently a more detailed account of the work of the Section. As regards the entire Conference and the volume of *Proceedings* to be published later I should like to tell you of an enterprising bookseller who displays in his shop window an assortment of Bibles for sale. A large picture of David and Bathsheba in an interesting embrace is also exhibited, and the advertising slogan reads, "You have seen the film: now read the book." That is what I say: read the book.

First Impressions

Dr. RAYMOND WHITEHEAD, rapporteur for the Section, said: It is my function to summarize and assess the work of Section A; you will appreciate that all I can give you is first impressions, because of the abundance of the material and the lack of time for reflection. On reporting to you I shall speak as a representative member of the audience, as an attentive listener, and shall tell you not only the scope of our work, but also what I think about it.

Before going further, I must give you my strongest impression, and that is of the high quality of the speakers, both those who read the papers announced in the programme and those who contributed to the open discussions. The contributions, both long and short, gave evidence of learning and scholarship, of deep concern for the subjects, and were often also elegant, witty, or graceful. And may I also mention the courtesy shown towards each other by speakers who disagreed; our proceedings have been entirely free from acrimony; this fact I find most pleasing, and it made the conduct and management of our meetings a delightful experience for the Vice-President and myself.

[1] *British Medical Journal*, August 29, p. 454.

The assignment of Section A was to study the requirements for entry into medical schools—in more concrete terms, to consider the kind of men and women we most want in the medical profession, the nature and degree of the education they should have, and the qualities of both head and heart that make the best doctor. Our main subject was subdivided into four more restricted topics—namely, general education, admission requirements of a scholastic nature, the scope and methods of teaching of premedical subjects, and the ways of selecting students.

Before I discuss and assess the contributions, it will be helpful to indicate the range of the papers in the four fields I have just mentioned.

Under general education we considered the value of ordinary—that is, non-medical—history; the value of ethical and aesthetic training; specialization in work at school; the influence of popular standards on university standards in modern democratic societies; and the decline of interest in Latin and Greek studies.

On the subject of admission requirements, we had most helpful reviews on current practice in the United States of America, the United Kingdom, Italy, Israel, and Mexico.

On the premedical subjects we heard the opinions of distinguished teachers of medical history, the history of science, scientific method, mathematics, biology, physics, chemistry, and the social sciences.

On the selection of students we considered the methods used in the United States, Australia, the United Kingdom, India, Canada, and the Philippines, and the more specialized individual topics of intelligence tests, aptitude tests, and the interview.

This brief outline shows you the scope of our discussions. I shall make no attempt to review the opinions of individual speakers—that would not be practicable in the short time available, and in any case they would be fairly assessed only against the background of the detailed evidence presented in the original papers. Instead of that, I shall give you the "sense of the meeting," as we call it—the general reaction of the audience to selected topics, as shown by the remarks of the discussers and by the facial expressions or other physical manifestations of pleasure of the listeners, which I was in a good position to see. If I have misjudged the reaction in some cases, those who speak after me during this plenary session will be able to correct my interpretations.

General Education

First of all, then, let me deal with general education, or what the prospective medical student can most usefully study while still at school. The case for the humanities—Greek, Latin, history, philosophy, the arts, music, and so forth—was put strongly, but Section A reacted against the idea (perhaps implicit) that science is in some way inferior to the humanities as an instrument of education. We all appreciated the value of the non-science subjects I have mentioned, but we also thought that science itself has a high cultural value, which is not yet sufficiently appreciated by the arts men. One of the main difficulties, however, is not any disagreement about the relative values of arts and science, but the purely practical one of lack of time to study all that is theoretically desirable. This lack of time is a most important point, and I shall come back to it again. Moreover, Section A recognized that there are great differences in the artistic and scientific abilities of different students, and that we should remember this more often when planning premedical curricula. If the admission requirements are too rigid, we may discourage the gifted arts man or deter even those with scientific abilities. We think special arrangements should be made to enable suitable graduates in other faculties to study medicine.

To sum up, there is complete agreement on the need of a good general education for the future medical student. The only differences are differences of emphasis on various subjects.

Admission Requirements

Our second topic, admission requirements, represents the translation into practice of the educational ideas and philosophies of the medical faculties—in other words, we proceed from the question of "What subject?" to the question of "How much?" A great landmark in this matter is the standard set when the Johns Hopkins medical school opened its doors. This showed that irrespective of demands for admission one can set a standard. Nowadays almost everywhere there is great pressure on the medical schools, which can not only fix a minimum standard, but can exact far more than is absolutely essential for the study of medicine. We have indeed a sellers' market and can be as "choosy" as we like. With so many applicants to choose from, we can be sure of good ability and plenty of knowledge. At the same time, we now give much attention to the general personality of the student—his moral qualities, such as honesty and tenacity. Besides testing his knowledge by examination, we therefore use technical devices to assess his personality.

Selection of Students

The selection of students (our fourth topic) is so closely linked with admission requirements that I discuss it now, leaving the third topic till the end. Section A heard of many methods now being used for selection. This was by far the most popular discussion of the week, and the contributions reached a high level, producing demonstrations of enthusiasm. All I can say on this subject is that every method is found useful by somebody, but none by everyone. The discussion will be most valuable in encouraging a review of one's own methods of selection and in stimulating schools that do not use available methods to study them. It is important for each country to relate intake to wastage in the profession. If we produce too many doctors, a serious decline of interest may follow and necessitate a fresh review of admission requirements and methods of selection.

I now turn to our discussions of individual premedical subjects. The speakers very ably expounded the value and importance of their own subjects. Section A heard these expositions sympathetically. It needed no convincing of the importance of mathematics, scientific method, biology, physics, and chemistry. The question here was not, "What subjects?" but, "How much?" Section A reacted against the idea of more mathematics, or more advanced mathematics, because many satisfactory medical students have only modest mathematical ability. An advanced knowledge of mathematics and other premedical subjects may be valuable to the doctor, or at any rate the research worker, but the bare solution of this problem is to collaborate with experts in the sciences, which is in fact what many of us do. In chemistry the need is not for more but for better co-ordination of chemical teaching, and Section A heard of successful examples.

On the social sciences—human anthropology and ecology—the audience had nothing to say, but we understand the speaker got some useful data from watching our behaviour in class and at coffee. The social services are too new for us to form any judgment as to their value for the premedical student.

Teaching the History of Medicine

The only controversial subject was that of the history of medicine. Section A held widely different views both as to its value and as to the methods of teaching it. One speaker thought it of supreme importance, the very foundation of all medical studies; another thought it of no interest whatever. The middle view was that it is very valuable for those students who may have a historical bent. For students who have no such bent, the subject is a waste of time. Perhaps much depends on the way the student is introduced to the subject. Few of us can fail to be interested in the lives of great doctors—one need not even be a medical student for that—and Section A agreed with one speaker that medi-

cal biography is the best introduction, perhaps by demonstration and exhibition, and we must remember that much historical teaching is given incidentally by teachers of any subject—the student does not know he is getting it. Experience shows that the teaching of the history of special branches of medicine is useful only when the student is perfectly familiar with the current knowledge of the subject. History is in fact explanation, and the student must first know what is to be explained.

With these remarks I come to the end of my formal review of our work. But I assume you would not wish me to sit down before giving you a few personal reflections of a more general kind. The ideas I shall mention have constantly recurred in my mind in the course of our meeting, and express the main benefit that I have gained from attending Section A.

Expecting too Much from the Student

My first point is that, personally, I think we expect far too much of the prospective medical student. From years of experience and reflection, we teachers have constructed an idealistic picture of the perfect student. I have heard several descriptions of the ideal student during our meeting, but none quite so brilliant as the satirical one of Professor Samson Wright, uttered last year. According to Wright, the ideal student is "tall, handsome, of great personal integrity, beautifully mannered, cultured, highly intelligent, a tireless worker, original, good with his hands, skilful in expertise, a good mixer, athletic, devoting his spare time to extramural activities, with a good family background, and so on and so forth." That, I suggest to you, is not a medical student but a Greek god, or at least one of those charming boys who bewitched Socrates. Let us remember that students are merely ourselves when young. Let us remember our own deficiencies, intellectual and moral, and be content if we see only one or two divine attributes in our prospective students.

My second point is that teachers are so busy teaching, lecturing, demonstrating, giving tutorial classes, and so on that the student has all too little time to learn for himself—and self-education is really the only education. Let us be more self-effacing and let the student learn more from his own mistakes.

My final point is that medical students (although they do not think so) are of necessity young and immature, lacking the great experiences of adult life. These experiences, both sweet and bitter, are what make both a good man and a good doctor, they round off the sharp edges of learning. We teachers have had such experiences. In every dean's office I should like to see in letters of gold the following words of a great Frenchman, Maurice Chevalier: "At our age, we must be reasonable."

Cultural Values

A few other members of the Section gave their impressions. Dr. T. B. DAVIE (Vice-Chancellor of Capetown University) said that all were desirous of seeing that the doctor of the future had as good a basis of general education as they, the teachers, hoped they were showing themselves. But in drawing the attention of students to cultural studies of a general character they must not lose sight of the cultural value of the medical education itself.

On the question of preliminary training they were all agreed that there could be no question of the removal of the study of biology, chemistry, or physics from, not only the preliminary but the continued training of their students, but that it was important to realize that these subjects could be taught in two different ways—namely, as independent studies or as studies directed primarily to their medical aspects. Cultural studies also would have to continue right through, "if only to enable them to read their *British Medical Journal*." As to intelligence and aptitude tests, these, as so far devised, were not yet of undoubted value, but there was reason to think that if medical psychologists directed their attention to them in the future it would be possible to have tests of intelligence at the beginning, and to have aptitude tests at the end of the course to suggest the degree of suitability for the specialties which the student wished to follow.

Dr. DONALD G. ANDERSON (American Medical Association) said that the value of the interview in selecting students for medical schools had not been placed very high by those who had discussed the subject in the Section. In the United States, on the other hand, it had been brought out that since the schools had been using the interview as a part of their regulations the faculties had felt that they were getting much better students and fewer student failures.

Dr. DAG KNUTSON (Chairman of Council, World Medical Association) referred to the need for keeping in view the relation between the numbers in the medical profession and the needs of the community. He had tried in Sweden to bring the "producers" of medical man-power into contact with the "consumers." Too few doctors were a danger to the community, but too many doctors were equally a danger because the quality was likely to suffer.

Dr. S. C. SEN (Secretary, Indian Medical Association) said that in determining the requirements for entry into the medical profession some sort of formula would have to be devised as to how much could be assimilated and retained. "The more we are taught the more we forget." It was said that the object of education was to produce a cultured gentleman. But culture was very difficult to define. It might mean a superficial veneer. He had pleaded for the teaching of the code of medical ethics, to which the World Medical Association attached great importance; but he had been told that it was not necessary to teach ethics, and that example was better than precept. He would suggest that professors and teachers lived in the ivory towers of education. If example was good, a little precept might work even better, and he hoped professorial members of the profession would listen to the field worker, who realized the importance of such instruction.

A few words in appreciation of the lessons of the Conference were added by Dr. M. POUMAILLOUX (Paris).

SECTION B: AIMS AND CONTENT OF THE MEDICAL CURRICULUM

Sir A. L. MUDALIAR (Vice-Chancellor, University of Madras), who presided over Section B, spoke as follows:

There was no Security Council atmosphere, to which the Chairman of Section A has referred, in the proceedings of Section B. Our proceedings were quiet, and the unanimity which obtained between the speakers was remarkable. I was myself greatly interested and surprised to find that they came from 25 different countries and represented at least 40 different medical institutions. It is a hopeful sign of the times that all of them should have felt the need for some revision of the ideas concerning educational development.

I can best give a few impressions I received from the papers and the following discussions, and Dr. Morgan Jones will follow with a more complete summary in his own inimitable manner. Anything that I say which appears to be in contradiction with his statements, please dismiss from your minds, and accept Dr. Morgan Jones's version.

We naturally discussed first of all the preclinical teaching and then the clinical. It was a great delight to me to find that the teachers of anatomy thought that much of what had hitherto been taught under that heading was quite unnecessary. The teaching of anatomy should be so conducted that the student would realize its ultimate purpose, and this should be more and more appreciated as the course goes on. Anatomy may have to be taught at three different levels—to the undergraduate, to the postgraduate, and to the specialist who would like to take anatomy as a subject of

special study. I feel happy in the emphasis that was laid on the teaching of anatomy and on the need to point out its application to the later studies in medicine and surgery.

So far as the teaching of physiology is concerned, likewise it was emphasized that in such teaching there should be greater emphasis placed upon its practical utility in the further studies in the medical school. It was thought that it would be well if the student at this stage would occasionally look into the hospital ward and be shown what was normal and abnormal and the way in which abnormalities could be investigated. It was necessary from the point of view of subsequent teaching of endocrinology and also in the teaching of neurology.

A plea was made for the integration of the study of physiology and of anatomy. This is a very practical problem. It was felt that if such integration were brought about it would be good for the student, save time, and make for greater emphasis upon both subjects. Conference between the teachers of anatomy and physiology was called for.

This naturally led on to the subject of pathology, and it was good to hear that pathology was not considered to be just morbid anatomy, but something far more important and interesting. It was urged that the amount of useful contact would be increased if the pathologist would walk into the wards and tell the students exactly what he felt about the pathological condition, and also if the physician would find time occasionally to go into the pathological laboratory and the necropsy room: the bearings of this subject would then be better appreciated. It is sometimes mere geographical distance that separates the departments and prevents a close liaison between them; but far more important than the geographical distance is the psychological distance between department and department. It was good to learn from the participants in the discussion, on both the medical and the surgical side, that it was their opinion that they must come closer together and that there must be active co-operation one with another.

A point of some interest which arose in the Section concerned the teaching of specialties. The specialties are increasing in number, and in the medical schools everybody who is practising a specialty thinks that it should come into the curriculum of the undergraduate. I do not know when the number of such studies will reach the point of excess. Some so-called specialties diminish in value with therapeutic advances. It is important that the study of specialties should be so balanced that we do not take a lopsided view. One speaker went so far as to say that the specialists should confine their teaching of their specialty to the postgraduate period. Whether that view will commend itself or not I do not know, but it is good to have some emphasis laid upon the fact that the specialties must have some limitation.

The Intern Year

One of the important points raised in the discussion concerned the intern year. In Great Britain it is considered absolutely necessary that the student should spend one year as an internee—six months in medicine and six months in surgery. Other countries are following suit, and the importance of this is reflected in the whole undergraduate curriculum. It is in that year, I think, that some of the specialties in which the student is interested will be taken further than is absolutely necessary for the undergraduate.

A discussion followed on the undergraduate and general practice. Here the general practitioners attended the Section in sufficient numbers to give expression to their full conviction as to the part which the general practitioner should take in the teaching of the undergraduate. That is a matter which has not been settled, but it is well for us to realize that the bulk of our students are likely to go into general practice and need not necessarily specialize. Therefore the need for ancillary methods of education designed to make them good general practitioners must necessarily be borne in mind.

There was a delightful discourse on the balanced curriculum, but I feel that I must take time to read it over and over again. So far as teaching hospitals are concerned there must be some arrangement in the admission of patients whereby properly integrated instruction for the student may be covered.

Lastly, let us remember the progress of medicine. What I learned 50 years ago I dare not repeat to-day. The stimulus of advancing knowledge must somehow be conveyed to the undergraduate. I have been connected with the teaching of obstetrics and gynaecology. I remember a surgeon who, coming in when I was operating, said, "You are dealing with the cesspool of humanity." I entirely disagreed with him, but the subject of obstetrics and gynaecology has to be realized as an important one in undergraduate medical study, because wherever the doctor may go I think I am right in saying that pregnancy and parturition, though physiologically normal, are pandemic. The need, therefore, for some knowledge of obstetrics and gynaecology by all practitioners is agreed.

I am sure from all these lectures and from what we have experienced this week we have reached the conclusion which I used to give my students: that all that we have seen is not to be compared with what we have yet to see. Having realized that, we have understood the subject.

The Basic Doctor

Dr. A. MORGAN JONES, rapporteur for Section B, said:

Some of my statistically minded friends have estimated that something near a quarter of a million words have been spoken in Section B, so I propose to confine what I have to say to the general ideas upon the approach to a planned curriculum which have emerged with a fair measure of agreement from the week's discussions. I hope you will endorse my view that it is not possible to attempt to enumerate the names of the very large number of people who have expressed the views I shall quote.

First, upon the aim of the curriculum. This is not, of course, identical with the aim of medical education, but it is so closely related to it that what appears to be the general view of the aim of medical education must first be stated. This is to produce what the Vice-President of our Section called the basic doctor; one who is neither physician nor surgeon, radiologist, medical administrator, nor even general practitioner, but an intelligent, educated, thinking man who has reached a stage of vocational training which will enable him to acquire more readily the necessary additional knowledge for whichever of the branches of medicine his inclinations and potential ability dictate. He should possess, first, certain qualities of character—integrity, conscientiousness, humanity, and unselfishness; then, certain attributes of mind—a genuine desire to learn, the knowledge of how to learn, and that sort of critical appreciation which Sir Richard Livingstone described as "the philosophy of the first-rate," whether it be first-rate in medicine or in life. Finally, he should have reached an adequate standard of vocational training, which implies a clear and well-digested acquaintance with the essentials of the main branches of medical knowledge—medicine, surgery, obstetrics and gynaecology—firmly based upon an appreciation of scientific method and a knowledge of normal and abnormal structure and function in man.

It is clear that the design and teaching of the medical curriculum can play a major part in determining the success of vocational training, and it can have an important function in developing the qualities of mind which are characteristic of an educated man. But the curriculum cannot greatly influence those inherent features of character without which the student is unlikely to make a first-rate doctor. For these we must depend partly upon the skill with which applicants for entry to the profession are selected, and partly upon the personal example of teachers.

Education and Vocational Training

I now turn to an analysis of the views which have been expressed upon the sort of medical curriculum likely to succeed in the twin aims of education and vocational train-

ing. It seems to be agreed that we are not very successful in either of these aims, and the principal reason for this is the growth of medical knowledge, which has vastly increased the factual content of the curriculum and has led to the fragmentation of the old primary teaching subjects into numerous sciences whose exponents all naturally believe in the great importance of their own field and strive to persuade their colleagues that more and more time should be devoted to it. All speakers seem to be agreed that the time has come to call a halt; to place the whole before the part, and to reunite the disintegrated fragments—in a word, to make the curriculum comprehensible once again.

The first task is therefore to simplify and unify the curriculum, and to this end many constructive suggestions have been made. The anatomists consider that the essentials of anatomy can be taught in three terms instead of five, though opinions differ upon the need for the student to dissect the whole body himself. Both anatomists and physiologists agree about the desirability of co-ordinating teaching in these subjects into a single joint course, and we have had the advantage of knowing that this reform is both practical and highly successful at Birmingham. Perhaps the most important suggestions about the content of the combined course are, first, that anatomy should be taught so far as possible on the living subject and should include much more radiological anatomy, and, second, that physiology should be based as much as possible upon experiments in human subjects by clinical methods. The combined course would include the usual clinical methods of examination, both manual and instrumental. The whole course should form a basis for the teaching of accurate observation and logical deduction.

If such a combined course in anatomy and physiology is adopted, it would follow that the essentials of physiology would also have to be covered in three terms. Subsequent courses in special anatomy and physiology would be necessary and would carry over the teaching into the clinical years, serving to keep these basic sciences before the student during the study of pathology, bacteriology, pharmacology, and the clinical subjects.

The integration of teaching during the clinical years is a much more complex affair. Most speakers are in favour of introducing students to the main clinical subjects and to pathology, bacteriology, and pharmacology in an "introductory" or "basic" course which would provide a broad view of the modern approach to the study of disease processes and to the principles of modern therapeutics. At this time, during what would be the second year of the medical course, the student would be introduced to the patient. Opinion is strongly in favour of emphasizing at this stage that the aim of medicine is to study and treat the sick person and not only the disease; that the problems of the sick person are closely bound up with personality and environment, social and economic. In fact, to make teaching "person-centred," not "disease-centred." To be truly successful this very broad basis of approach must dominate the outlook of teacher and student from the very first contact with the sick person.

Many useful suggestions have been made to help the student to appreciate the place of the individual in the family and in the community, as, for instance, visits at this early stage to antenatal and child welfare clinics and to the home of the sick person. The general practitioner may well have a place at this stage, for we were all impressed by the reproach of a medical student that we make the student familiar with all fields of practice except general practice. Such an introductory or basic course would be far more comprehensive and broad in outlook than the introductory course usual in most medical schools, and it could scarcely take much less than a year.

Joint Courses

If we accept this sort of plan for the first two years of the medical course the outline of subsequent years is fairly plain. The task of the anatomist, the physiologist, the pathologist, and the pharmacologist has only started. It has, I think, been in the minds of many that we might with advantage systematize the theoretical study of disease processes of, say, the heart, or nervous system, by joint courses in which the anatomy, physiology, pathology, diagnosis and therapeutics, including surgery, were jointly taught. In such courses lies, perhaps, the best educational function of the system specialist, cardiologist, neurologist, and so on. From a logical and educational point of view this seems admirable, but if it is applied to the practice of medicine it leads only to another form of fragmentation. If courses of this sort are to be used for theoretical teaching it must be clearly borne in mind that their aim is to join the basic sciences to clinical medicine and to provide a convincing demonstration of the application of scientific methods to the diagnosis and treatment of disease. They are not a means of learning how to treat the sick person or how to handle the patients' psychological, environmental, social, occupational, and economic problems. For the study of the practice of medicine in its broader aspects there is no substitute for clinical clerkships, out-patient clinical work, and the study of the patient in his home and occupational environment. We must never again allow these aspects of medical training to be strangled by a growing preoccupation with scientific medicine.

It may well be that we can profitably synthesize the medical and surgical clerkships. Many feel that the best surgeons have much to offer in their approach to the patient and in the application of science to diagnosis and treatment. But although the student must be aware of the possibilities and scope of modern surgery there is no justification for trying to teach details of surgical technique which are usually sparingly gleaned during hours of intellectual idleness in operating theatres. A limited experiment in joint teaching at Birmingham has helped to reveal some of the conditions which make for success. In all such co-operative efforts, however, it is essential for physician and surgeon each to preserve his intellectual independence and to seek every opportunity for joint consultation and discussion.

Consideration of the teaching of minor surgery emphasized the opportunities which this subject presents to teach the principles of surgery and the personal problems of the injured man.

Teaching needs in obstetrics clearly differ widely in the countries represented here. When doctors are widely separated and consultants inaccessible much greater prominence must be given to technical obstetrical competence, but it is fair to say that in most countries there is an increasing tendency to childbirth in institutions under the care of physicians who have had postgraduate training in obstetrical technique. In undergraduate training we are therefore likely to become increasingly concerned with the study of the antenatal and postnatal care of the pregnant woman, and with the general study of the physical, psychological, and social problems of child-bearing. Such teaching gives ample opportunity for developing a broad humanistic approach to the patient.

In paediatrics we were subjected to a logically planned intellectual assault of almost stultifying proportions. This carried great conviction. There is, however, one commonly used argument which should be viewed with suspicion—the argument that the time devoted to a subject should be proportional to its frequency in practice. There is, however, no proportional relationship between the amount of knowledge required to treat a condition and the number of times it has to be treated. Of course it is true that any common conditions should be adequately studied, but the time required for this depends upon how much of value there is to learn about it and not upon its frequency in practice. In paediatrics, of course, there is much to learn of lasting value. And, personally, I would give my wholehearted support to the educational activities of any paediatrician who, like the speaker who opened this discussion, has the courage to claim that he is prepared to dispense with the paediatric portion of the final examination and still guarantee that his subject will capture the student's interest and enthusiasm.

Upon the specialties of dermatology, ophthalmology, and oto-rhino-laryngology little has been said. All are agreed that they must be restrained in their demands, but opinion is divided upon whether it is better to limit them by rationing their teaching time or by trying to incorporate them in the teaching of their parent subjects of medicine and surgery.

Psychological Medicine

I now come to the controversial topic of psychological medicine, upon which much has been said. It will be agreed by everyone that the problems of psychological medicine must pervade the whole of medical education, just as they pervade the work of every practising clinician, whatever his line of work. We can also agree that we owe a great deal to psychiatrists and psychologists for a better understanding of our task in treating the sick person. The time devoted by every clinical teacher to this aspect of medicine should be considerable. But many are not so sure that much time should be given to more formal systematized teaching by psychiatrists, and the importance of the subject is not an argument for this. This conference has set its face against the progressive disintegration of the teaching of the main subjects to undergraduates, and it is to be hoped that we can minimize this tendency in the case of psychological medicine. Everyone would, however, welcome a course on general psychological medicine which embodied the very broad-minded and tolerant approach adopted by our opening speaker on this subject.

In the address on tropical medicine we were given an example of how much a wise and tolerant attitude by a specialist can help in the integration of medical teaching. It was suggested that in temperate countries no separate course was necessary and that the desirable teaching could be incorporated into physiology, clinical pathology, pharmacology, and the differential diagnosis of medical and surgical conditions.

The compulsory year as an intern was generally welcomed, and I think most people feel that this guarantee of post-graduate vocational training might help to make room in the undergraduate course for more activities of an educational nature.

Active Learning

The last part of what I have to say deals with those suggestions which have been made with the object of improving the educational as distinct from the vocational aspects of the curriculum. The essential prerequisites for education are a genuine desire to learn and a sound knowledge of *how* to learn. It has been said that man can learn almost anything, but he can be taught almost nothing of real value except how to learn. True education is self-education. (I offer no excuse for the repetition of these platitudes, because I think they cannot be repeated too often.) Most teaching methods of truly educational value aim at teaching the student to think for himself, and what the student gains from them is strictly proportional to the effort he makes. Further, as Sir Richard Livingstone pointed out, true education implies the ability to express what is learnt. It is with these ideas in mind that many valuable suggestions have been made during these proceedings. It is from the interplay of one mind with another that the stimulus to critical thought comes. Consequently, teaching of small groups of students is always more productive than formal lecturing, and all types of discussion classes are better than didactic teaching. It has therefore been suggested that clinico-physiological and clinico-pathological conferences are not widely enough used, at least in this country. In these the student must be encouraged to play an active part, for this stimulates him to think and trains him to express what he thinks.

To simplify and unify the curriculum is in itself valuable educationally, first, because it helps to give the student a co-ordinated body of related essential facts as a basis for critical thought, without stultifying his capacity to think by a mass of memorized unrelated details. In addition, it must bring together teachers with different points of view, and even to hear intelligent discussion between teachers in itself provides a stimulus to the student to think. Activities such as preparing a critical account of the present state of knowledge of a limited subject and presenting this to his fellow-students for discussion encourage the student to develop his powers of critical appreciation. Personally, I regret that we have not followed up Sir Lionel Whitby's suggestion of a tutorial system in medical education, for, although expensive in time and staff, this method provides the best-tried technique we know for true education. Another point which seems to have largely escaped our attention is the importance of leaving an adequate amount of free time for independent study, especially towards the end of the course, when the student should know how to go about learning for himself.

After listening carefully to so many stimulating papers by great authorities on medical education throughout the world, I am left with the impression that most are not in serious doubt about the sort of general lines upon which the medical curriculum could be modified to bring it into line with the present stage of medical progress and to enhance its educational value. We are naturally apprehensive of the upheaval which reform would entail, of the many adjustments of our teaching practice, and of the personal difficulties and resentments which might follow. If this conference has served to strengthen our conviction of the necessity for reform and has brought some of us to the point at which we are prepared to face the consequences, it will have served a most valuable purpose.

Dr. OLIVER COPE (Harvard) stressed the danger of specialization. He thought they should take back into the general fold of surgery the surgical specialties. Urology, oto-rhino-laryngology, and gynaecology would be easy; orthopaedics and neurosurgery rather harder. Professor W. LÖFFLER (Switzerland) said that lectures seemed to be becoming an obsolete form of clinical training, but they could not abolish them. Dr. H. G. WEISKOTTEN (American Medical Association) said that the real problem was to re-integrate undergraduate medical education, which had become disintegrated as medicine developed.

SECTION C: TECHNIQUE AND METHODS IN MEDICAL EDUCATION

Professor A. HURTADO (Faculty of Medicine, University of San Marcos, Peru), who presided over Section C, spoke in Spanish, and the following is a translation of his speech:

In Section C, which discussed technique and methods in medical education, various subjects have been reviewed by expert speakers. They may be enumerated as follows: teaching in the hospital, the clinic, and the home; the clinico-pathological conference and work in the laboratory; visual aids such as lantern slides and films; the lecture and the group discussion; textbooks, libraries, and museums; the training of the teacher; and, lastly, why students fail. In regard to the last of these subjects, we were fortunate in being able to hear the opinion of one of the students who attended this Section.

As all the teaching techniques and methods which are employed depend on the curriculum and other aspects of medical education, we cannot rule out the possibility that some of these subjects have also been considered by other Sections. Following the procedure adopted yesterday, I will leave to our very capable and efficient rapporteur, Professor Ian Aird, the detailed consideration of the communications, and during these few minutes will confine myself to a few general points on which there was not unanimity. This does not mean that the aspects which I do not mention have not equal or even greater importance.

The Basic Training

One of the questions asked was as follows: As it is certain that the great majority of the students will eventu-

ally enter the profession as general practitioners, should medical education be directed in the main towards this end? Or should the education rather be of a general nature, so as to make the student familiar with the most important scientific facts in all branches of medicine, leaving the final specialized instruction and orientation until later?

This question was discussed at great length. We are entirely in agreement with the second alternative. We believe that training for general practice, just as for specialization, belongs to the postgraduate period. Whatever the branch of medicine, there is no substitute for a thorough scientific preparation and grounding in the basic knowledge necessary for all types of professional activity. We believe that it is wrong to orientate undergraduate instruction towards the requirements of closely defined future activities. Nor must we forget that the objects of medical education are not purely and simply the preparation of good doctors, whether general practitioners or specialists; it is during the student period that a vocation for teaching or a leaning towards research may be awakened. This can happen only within a general scientific framework during the acquisition of knowledge which is not closely tied to a fixed curriculum, and in a system of education characterized by the stimulus it gives to the student to think for himself and freely choose his future field of action.

The question of whether the student should carry out research was discussed. I do not know the answer to this. I do not know whether it is wise or not. However, if he does not carry out research himself to some limited extent, it will be helpful to discuss research problems with him. Very early in his career the student must learn that one of the fundamental characteristics of medicine is its changing nature and the enormous number of observed facts and mechanisms which we cannot explain compared with those we can. Moreover, there is nothing better for curbing a smug feeling of self-sufficiency and an exaggerated opinion of one's own importance—so frequent in youth and not very rare in later years—than knowing that there are so many questions as yet unanswered.

All were agreed on the value of using out-patient clinics, and even the home, in addition to the hospital ward, as places of instruction, so as to familiarize the student with certain aspects of his future professional activities.

There was a lengthy discussion on the comparative merits of the full-time and part-time teachers. There was agreement that full-time teachers were necessary for preclinical courses. Where the controversy arises is in regard to the clinical courses. It is our belief that here full-time teaching need not be adopted as an invariable rule. On the other hand, it is unwise to reject it out of hand in those cases where personal inclination favours it. It was agreed that it is unsuitable because the full-time teacher is a physical and intellectual prisoner and he lacks the important quality of knowing how to assess and treat a patient who is not in hospital. But we asked ourselves the question: Is instruction in medicine and surgery or in any other branch imparted solely and exclusively by the principal professor or other member of the full-time staff? If such a person is unable to instruct the student in some particular aspect of medicine, then doubtless there will be someone on the staff who can. Furthermore, the full-time professor is by no means an intellectual prisoner. There is prevalent a mistaken idea on this point. Such a professor may give lectures outside his own university, attend academic gatherings and meetings of learned institutions, write books, and travel, and, what is most important of all, he has the time if he so desires to carry on research. There is nothing more contrary to mental imprisonment than the pursuit of new knowledge.

Personal Contact

We discussed the comparative value in medical education of lectures and group discussions. No one doubts the importance of the latter in establishing the proper personal contact between teaching staff and students. However, we must not forget that the lecture has very great value. It is not just a question of the way in which a certain subject is presented or discussed with a greater or less degree of clarity. In a lecture, the professor often teaches the students how to co-ordinate facts, express themselves, reason, and speak properly. And we must not overlook the fact that it is just as bad for medicine if instruction is purely practical as it is if entirely theoretical.

We would like to emphasize particularly the wisdom—or, more than this, the necessity—of establishing personal contact between teaching staff and students. This point was mentioned time and time again. In some of our universities this is impossible because a queer idea of educational democracy has opened the door to hundreds, and in some cases thousands, of students. If some recommendation is to be formulated at this Conference, nothing could be more fitting than one pointing out that the number of students in a faculty of medicine should comply strictly with the training requirements and the teaching capacity of the institution. Bearing in mind the responsibilities and duties of our profession, whatever may be the field in which they are to be exercised, we feel that this is an inescapable duty for those of us who are in contact with this problem in our respective countries.

I should like to mention briefly something that was not discussed: the importance of international co-operation in medical education. What a boon it would be if the fellowships offered by the institutions of the major countries were not restricted, as they generally are, to postgraduates interested in some particular clinical subject or line of research. The exchange of students, who after all are the teachers and heads of universities of the future, would result in a personal acquaintance with teaching methods, and a vivid experience of how teaching and learning are performed in other centres. I feel that this is highly desirable.

A Time for Experiment

Finally, I will take the libefty of making a brief point of a general nature. It is my impression of the work of this Section, after having heard what has taken place in the others, that there is unanimity in the belief that medical education is in need of reform and fresh planning. However, this unanimity does not obtain with regard to the various methods and processes which should be employed to this end. What is more, very few indeed of the methods that have been advanced to-day are backed by sufficient experience. These facts compel us to be cautious and even modest and to avoid praising or condemning this or that process too soon. Let us content ourselves with saying that the people and institutions of such and such a country use systems and methods of a different type, according to the requirements and characteristics of their particular part of the world, and let us express the hope that at the next World Conference the theories, hypotheses, and opinions of to-day will have been translated into facts which can then be analysed according to their results.

In conclusion I would say that it is extremely gratifying and encouraging to see that the teaching of our profession is entering upon a stage which is shared by all medical problems: the experimental stage. The working hypotheses have been formulated. All that is to be done is to test them out and to eliminate them one by one. This work of research has always been, and will continue to be, the path which will lead us to true answers.

Detailed Systems

Professor IAN AIRD, rapporteur for Section C, said:

We were a very happy Section. Our interests were rather mundane, not diffused with the starry ether of educational strategy: our hands were turned to polishing our ploughshares, but occasionally we saw reflected in them the stars.

Our work took the form, not of a developing philosophy, but of the successive presentations of detailed systems of educational technique and individual methods. Consequently my report must necessarily be a sketchy one. Many of our speakers undertook constructive and detailed accounts of systems of educational technique, and these do not lend themselves easily to abstraction without losing the whole background of their content. Therefore I shall limit myself to picking out some points which can more easily be presented shortly.

Professor A. Hurtado, our Chairman, was a genial and encouraging mentor. One point he made at the beginning of the Conference, and reported in the *British Medical Journal*,[1] is that the elimination of certain facts to make room for others cannot go on indefinitely. Knowledge does not advance by replacement only, but often by addition. To allow for this, preclinical and postgraduate training have been extended lately, but clinical not to the same extent.

Professor Hulst set a note of slight disquiet, repeated often later, that the young graduate was bound to meet in practice early and minor disease of which as a student trained wholly in hospital he could have had no experience. In later treatment of the patient at home, too, he would meet with environmental and family relationships with which he was unable to cope, and this might result in disillusion. Professor Poumailloux raised the question, "When should the student come in contact with the patient?" He felt that this should be early, even if he is to remain silent for a time, in order to learn how to avoid the constraint always induced in the healthy towards the sick and by the contact of the young student with the elderly patient. Professor Dorst attached importance to clinical clerkship, seldom found outside London.

Sir Geoffrey Jefferson expressed concern at the high percentage of failures in the final examination. He felt there must be something wrong somewhere. Other speakers quoted even higher figures. Sir Geoffrey Jefferson felt that not enough time was spent beside the bed. He disagreed mildly with the view that the whole of medicine is covered by psychiatry and biochemistry. He had known patients who were sick, though neither chemically nor mentally unbalanced. He thought that it was usually stupid to bring students into theatres *en masse*, but they should come in with their own patients to learn how meticulous surgical asepsis is, and to maintain continuity of understanding of their patient's progress. The surgeon could also take an opportunity of reminding the student of anatomical detail—and himself too, for surgeons proceeding down the operation road were often familiar with the streets without remembering their names. He also stressed the importance of amiability in the teacher. The silent surgeon was useless to the student. The surly surgeon was a bad influence. Not all the attributes of the fine teacher could be learnt by taking pains, but a "poisonous" manner could often be improved.

Dr. Neuffer made a good point when he reminded us how little the graduate is equipped to superintend the home nursing of his patients in practice, and urged that he be taught at least the elements of nursing detail.

The importance of out-patient teaching for students, the majority of whom will be general practitioners, was stressed by many speakers. Dr. Dag Knutson and others regarded even the stress of time which is imposed on most polyclinics as likely to encourage an economy of time which would be valuable to the graduate later in general practice. It would show him how to use his consulting time to the best advantage; though Dr. Husfeldt warned against too great a pressure of work and to avoid contrast between carefulness in the wards and carelessness in the polyclinic.

Mr. Ewing noted the importance of the follow-up of the patient in the polyclinic after the operation, just at the time after discharge, when the general practitioner may have to detect complications. Dr. Chiari told us how in the polyclinic in Vienna great dependence is placed on ear and eye as diagnostic instruments, and how the student visits the patient at home with the family doctor. The out-patient surgeon or physician must be senior, highly qualified, experienced, widely informed over a broad field, and humane. Dr. Ransome reported the interesting practice at Singapore of having in the polyclinic a chemical and haematological laboratory, facilities for clinical pathology and bacteriology, *x*-ray apparatus, electrocardiograph, and endoscopic tools, all with technical assistance, so that students could learn to make accurate, on-the-spot diagnosis.

[1] *British Medical Journal*, August 29, p. 469.

Home Teaching

Several reports were submitted of attempts to teach directly the care of patients in their own homes. Dr. Kinlock Nelson described the Virginia experiment in which the district poor came under the care of the university faculty. A team of clinical director, two part-time assistants, house officers, administrative and social workers, telephone operator, nurse, secretaries, and a statistician, with eight or ten medical students, gives a whole-time service, complete with automobiles and radio-telephones. The health department and sanitation bureau come in when required. British schemes were described in which students accompany selected practitioners for a time in their consulting-rooms and in the patients' homes, not to learn the technique of general practice, for that can be learnt only after graduation, but by some such scheme as the Government has devised for placing trainee practitioners as apprentices with selected family doctors. The idea is to attract students to general practice and to show them how good general practice can be. Of the 21 medical schools in the United Kingdom, general practice schemes are organized in nine.

The value of the clinico-pathological conference was generally agreed. It was shown how the clinico-pathological conference could be adapted for the demonstration of recent operation specimens and for discussion at staff level. Professor G. A. Elliott advised that separate conferences be held, one for each clinical year of students; it was rewarding to see the development of the student mind from year to year. Professors Garreton-Silva and Soriano reminded us how helpful to the educator and to the community is the legal requirement in some South American countries of necropsy in the case of all deaths, and Professor Hurtado described the clinico-physiological conference in which young students are shown functional abnormalities in out-patients, with no mention of pathology or diagnosis.

The next title, "The laboratory in teaching experimental medicine," was the only title in our sectional programme which left room for doubt about its precise intention, and speakers interpreted it differently. Dr. John W. Patterson described a new teaching programme at Western Reserve University which attempts to inculcate in students a desire for and introduction to the habit of research. There is no time here for me to describe in detail the three phases into which the programme is divided, and only phase I, corresponding to the first year, has so far been completed. In this, to encourage self-education, the student receives an introduction to library methods and to biostatistics, works on a given laboratory experiment or exercise, and is afforded free time to follow some private project of his own in one of the basic sciences. But I think that the general opinion was that research should not be undertaken by undergraduates. Professor Garrod recommended that students should have as much laboratory work as possible so that later they will know what material they should send to the laboratory, will gain some technical facility, and also have the educational advantage of making even bad specimens for themselves. He thought students should carry out procedures on each other—performance of the Schick test, for example, and the taking of swabs—and be encouraged to bring material from the operating theatre or post-mortem room to section themselves.

Professor Garrod also reminded us that in this country students—undergraduate or postgraduate—are forbidden to gain experience by operating on animals. Delegates from abroad were surprised to learn that young surgeons here must perform their first operations, in any field, directly on human patients. Dr. Jean Vinter, secretary of the Universities Federation for Animal Welfare, urged that experimental animals be treated with the same consideration as human patients; and a later speaker, Dr. Lillie, went rather further than this in his feeling for the animal world.

Visual Aids

The morning devoted to the use of visual aids in medical education was quite fascinating. Dr. Cardew urged the careful co-ordination of the work of photographer, artist, and projectionist with that of the teacher, and on grounds of efficiency and economy recommended the grouping of all illustrators under a common director. He and, later, Miss S. Treadgold showed how the museum could be combined with the library by arranging illustrations in book form. Dr. Cardew condemned much of the projection apparatus used in medical schools, and recommended the adoption of the various national standards of screen brightness. Investigation by Harrison had shown that in the lecture theatres of a British medical school the best screens were 45 times better than the worst.

Mr. R. P. Creer gave a brilliant demonstration of the use of the cinematograph to record and demonstrate endoscopic findings, but later speakers warned against the indiscriminate use of the cinematograph. Dr. Cardew had stressed the infinite care required—and at university level—to make sure the film actually taught, and Dr. Howard Hughes recommended its use only in short lengths as an "animated slide." I ventured the opinion that films were most useful in surgery to display gaits and other kinetic physical signs, and, surprisingly, disease of the oropharyngeal and other mucosae, and that most clinical and operational films failed to hit the correct tempo to ensure understanding and to avoid boredom. It is only fair to say, however, that Mr. A. B. Gilmour, a medical student, reported that medical students liked them, particularly if they had an opportunity of seeing them run through twice.

The cost of filming is high. Dr. Collard suggested that the cost could be cut if not only departments but faculties co-operated. Several speakers urged the formation of a central film unit, and Professor Robert Cruickshank reminded us of the existence of the Medical Committee of the British Scientific Film Association. There is also a Unesco agreement for facilitating international circulation of visual and auditory educational material, payments being arranged by Unesco coupon. Our Section agreed that more than this should be done, and that W.H.O. be approached to consider the establishment of an international medical film index for world distribution.

Dr. Tom Jones gave us a feast of "still" pictures, which he proved to us to be the most generally effective and available visual aid to education, though, as he and others pointed out, a variety of visual techniques, including the lowly blackboard, must be available if full advantage is to be gained from illustration. In the teaching of medical history the advantage of pictures hung on walls and corridors and changed every few weeks was reported. Most of Dr. Jones's line diagrams are now of white or colour against black, and most of his printing is done by electric typewriter, which photographs well, but, as Dr. Ollerenshaw pointed out, the British student prefers black on white, perhaps because his notebook is better illuminated even by the dimmed roof light which modern projection methods usually permit.

A beautiful feature of this programme was Dr. Leake's demonstration of the value of the cinematograph applied to phase contrast microscopy and tissue culture. The curious tempo characteristics of cine-photography are here an advantage in affording a contrast record of cellular behaviour. The picture of mitosis and cell division is a classic. The one-way screen for students to see without being seen may have ethical disadvantages, but these are no different from those of the operating theatre.

Group Discussion

Group discussion methods were explained by several experts. These methods, valuable in all other fields of education, since they permit multiple channel communication, are applicable to medicine. Indeed, these methods are familiar now in bedside teaching in clinics where the teacher has the gift of intimate conversational tuition and the benefit of a small class. It is valuable, however, to regard the technique of group teaching as a special one, if not a new one, in order to make available to all what has in the past been the attribute of the few. An essential element in it is that, except when deciding initially how much the students know, and later when adding something new to their knowledge, the teacher descends from the *cathedra* and allows them to argue and discuss, merely correcting their errors and guiding the direction of their common flow of thought.

Professor Soriano, like many other teachers, permits questions at the end of lectures, but our educationalist advisers do not admit that question time is a substitute for group discussion.

The Whole-time Teacher

Dr. L. T. Coggeshall and Dr. Wulff spoke strongly of the advantages of strictly whole-time university service such as obtains in the University of Chicago, all professional fees reverting to the university. They reported that not only the students but the patients appreciated the high standards achieved by a combination of medical care, teaching, and research.

Subsequent speakers from the Americas and the Continent were all opposed to the strict whole-time principle on these damning grounds: the whole-time man did not have an opportunity of seeing the patient against a background of real life; of seeing the patient in his own home; of seeing the whole patient. On the one hand it was argued that the whole-time man did not get a sufficient practical experience of his own specialty, while on the other that his unusual skill in that specialty is not available for all sections of the community. A startlingly novel phrase, "The ivory tower," was used with effect more than once. That this wholesale criticism of the whole-time system is surprising to British ears was made clear by the remarks of Mr. Patey, who suggested that part of the difficulty of the whole-time scheme in places where it has been unsuccessful may be financial. Ideal schemes often fall down on finance. He suggested that the adequacy of the whole-time scheme in Britain might perhaps depend on the fact that there are no charity patients in England now. Indeed, strictly whole-time university teachers in most centres treat patients in all walks of life and must concern themselves with their families, and, in the case of public men, with the political implications of their illness too. None of us who advise on the filling of British chairs would recommend a laboratory research worker to a clinical chair any more than he would appoint an applicant devoid of training in research method or guiltless of original thought. It occurs to me that in Britain the establishment by the Medical Research Council of clinical research units within teaching hospitals, but without heavy clinical or teaching responsibilities, channels the pure research worker away from the main academic stream.

Mr. Patey added that the effect of the medical service has been to abolish the sharp distinction between part-time and whole-time. The whole-time man is highly paid for his whole-time work, and the part-time man is remunerated to spend as much as 86% of his week in hospital. The part-time man can be extremely active, as Mr. Patey has been, in teaching and original clinical work. There is great

harmony in this country, I believe, between the "tower" and the "citadel." The "ivory tower," now a little off-white and tarnished by acceptance of an economic wage, and the "golden citadel," a little less glittering, have occasional exchanges, not cannonades between the big brass on their battlements, but in the shape of impish arrows from the lower floors. The principle of whole-time chairs should not be condemned on the ground of clinical and educational inadequacy, but rather the close co-operation with our part-time colleagues which we here enjoy should be a matter of envy.

The Use of the Textbook

The use of the textbook in teaching was discussed by Professor Muller. Primarily as the commencement of an oral and practical course of study, correcting the teacher's errors of omission and commission, a manual for the undergraduate written by a single hand seemed to be preferred. It was said that the undergraduate, in his reading as in his curriculum, did not suffer if he subjected himself to the discipline of a single master.

Professor Debono found more difficulty in prescribing a single book, and quarrelled with the idea of a set prescribed book whose memorization, with or without understanding, would guarantee to guide its reader to graduation. He was ultimately forced to issue duplicated notes of the bare bones of his lecture course. It was urged that the out-of-date diagrams with obsolete methods of reproduction which sometimes "adorned" modern editions of older works should be replaced. Professor Debono regarded as the best "textbook" the notes prepared from textbooks by the student himself. I agree with this plan. The student cannot too early be taught how to construct a cross index to serve as an artificial memory.

The subject of libraries in medical teaching was well covered, as indeed it should be, as the most indispensable single department of a medical school. Colonel Rogers reminded us of the Americal Medical Association's requirements of a trained librarian, modern text and reference books, serviceable card indices, and leading medical periodicals regularly received. A survey in 1953 showed that the number of volumes in American medical school libraries ranged from 3,000 to 375,000, with a mean of 35,500, and a mean library budget of $25,000.

Mr. Barnard described the library course at the London School of Hygiene and Tropical Medicine. Instruction in library arrangement and usage and in the preparation of bibliographies, with practical exercises in the library, has much to recommend it. The student often has a feeling of revulsion at the vastness of a library when he first enters it, and some introduction is necessary. Good lighting and comfortable seating are essential.

Dr. Hackett's description of an ideal medical museum (the Wellcome Museum) was fascinating, but since every medical visitor to London visits the museum I need not repeat him in full. Several speakers raised the question of an international bureau and world index of demonstration material, and all who did so instanced Dr. Hackett as a suitable "accoucheur" for such a scheme. The Section would wish to record this as a most desirable project.

Dr. R. D. Lawrence on Thursday gave the results of the long thought he has given to medical teaching, and suggested the inception of courses for medical teachers. The Postgraduate School at Hammersmith is in process of arranging such a course for next year, when a group of young registrar volunteers from several universities will be given short tasks in lecturing, bedside teaching, group methods, and clinico-pathological conference work, their efforts being criticized constructively by a chosen expert in each of these media. Dr. Troupin severely criticized the choice of clinical teachers from laboratory workers.

On Friday we discussed examination methods. A suggestion that the examination paper be used to eliminate the worst candidates, as in the Membership examination of the Royal College of Physicians, was strongly rejected by subsequent speakers, who also disliked the London close-marking system. The useful suggestion was brought forward that examination papers should be made available to senior staff to help them assess the value of their teaching. There was no agreement on the superiority of external or internal examinations. I believe the latter suits better the universities conducted on predominantly departmental lines.

Dr. R. A. Moore awakened sharp interest in the multiple-question examination paper in an audience initially prejudiced against it. The framing of questions to cover not only a knowledge of simple facts but a combination of facts and reasoning showed much ingenuity, and his figures showed that such a paper correlated better with the estimate of the student's work in his medical school than did the traditional type of paper. Such papers can be analysed by electronic machinery, but there is no saving of time to the examiner. Time saved in correction does not compensate for the great amount of time spent in preparing questions.

Failed Students

Mr. Henn's paper on "Why students fail" reached the highest levels of philosophy, poetry, and inspiration. He estimated the financial cost of "losses" to the student body as £52,000-plus on an annual entry of 2,000. Among the causes of failure he placed (1) over-estimation of the amount of sound university material of the population, which he would estimate at only 15%; over-drilling by pre-university teachers and loss of the "temper" of the intellectual "steel"; (3) disinclination for a profession forced upon students by parents; (4) lack of power to concentrate, and ineffectualness of work; (5) lack of "fire" or natural curiosity, and boredom; (6) eyestrain; (7) physical handicaps; (8) external distractions (these do not seem very important); (9) internal distractions—love affairs, increasing class difference from the student's family, psychological disturbances such as masochism short of suicide. The correction of most of these depends on helping the student to know himself and recognize his place in the cosmos, endowing him with a philosophy or religion.

Professor Cameron added to the causes of failure, neurosis (with a "blow up" at examination time), a major change in ambition or aim, ability to work only in a state of anxiety so that reading is postponed until just before the examination, and doubt of his ability to pass, so that he ostentatiously avoids working and people say when he fails, "Bad luck, Joe, but you couldn't expect to pass." Thus he saves face. Women are particularly prone to physical or mental breakdown.

The soil in which our Section dug was a fruitful one. Occasionally the tone of our meetings was raised by a visitant from another Section, who came amongst us lightly powdered with star dust and happily intoxicated with ethereal eloquence and flicked off an angel's feather in the shape of a new idea. We were a happy Section, as I have said, and I should like to add how much I myself have learned in this Section concerning the art of teaching and the problems that arise in the medical educational field in this and other countries.

Professor A. GARRETON-SILVA (Chile) followed with a few remarks on the need of South America for many more good physicians. His country would make use of the knowledge gained at the Conference. Dr. P. N. CARDEW (St. Mary's Hospital) briefly reported on the session of the Section which was devoted to visual aids in teaching. In this field, he said, they suffered rather from the enthusiast who thought that the film could teach everything. He had an impression that teachers could take greater advantage of the illustration departments and seek their advice. The capabilities and limitations of each method had to be considered, and illustration should be used with greater precision than was done to-day. Some films which were most useful were difficult to obtain—for example, endoscopic films. The trouble was that teachers did not make their own films; they used films which were by-products of films made for advertisement. "Hollywood is no good to the

medical student." An international co-ordinating committee to act as a clearing house of information on films would be a great advantage. Distribution of films on a wide international basis would lessen what was now a considerable expense.

Professor R. A. MOORE (Washington University) spoke of the newer techniques which were being introduced into education in general. Medicine was not an exact science : the technique of its teaching must be learned and revised continually.

SECTION D: PREVENTIVE AND SOCIAL MEDICINE

Professor A. STAMPAR (Yugoslavia), who presided over Section D, spoke as follows:

It has been a great privilege for me to be asked by Sir Lionel Whitby to preside over the work of this Section discussing educational problems relating to preventive and social medicine—a great privilege not only because of the honour thus bestowed upon me but also because of the pleasure of seeing so many of my old friends whose work and struggle for the ideal of social medicine I have been following these last thirty years. I am also glad to say that I have learned quite a few things from the contributions made by our speakers, some of them very original, and that I have been cheered up by the progress social medicine is making as an academic discipline.

You know how difficult this path of preventive and social medicine has been, in spite of the developments in the course of the last two hundred years, not only in the progress achieved in the thought of the people writing about and applying social medicine, but also in the progress in practical matters such as the sanitation of big towns and industrial regions, and public health administration, which from year to year has been covering increasingly wide areas.

I vividly remember the first meeting of a small committee organized by the Health Organization of the League of Nations in the early 'twenties. It was preponderantly composed of representatives of classical medicine. Those looking upon social medicine as the medicine of the future were in a small minority. Several years had to pass before the Health Organization of the League started to discuss more thoroughly questions of medical education generally and the teaching of preventive and social medicine in particular. It was only then that the latter began to be approached as " collective medicine " and health as a collective and not only as an individual responsibility.

I think it should be put on record here that in the period between the two wars the Rockefeller Foundation gave material assistance to many universities in the U.S.A. and to many European health administrations and universities for the establishment of such institutions as schools of public health and institutes of hygiene. These were to become, and indeed became, the local centres for education and research work in the field of social medicine. The period between the two wars can thus shortly be summed up as the period of the struggle to secure for social medicine an appropriate place in the medical curriculum.

As in so many other fields, the second world war caused a set-back and stagnation of this development.

However, after the war, through the creation of the World Health Organization, a new impetus was given to the above development. An expert committee met in Geneva in 1950 ; the World Health Assembly chose medical education as the main theme of its technical discussions in 1951 ; an expert committee and a European conference on medical education met in Nancy in 1952 ; and an expert committee discussing postgraduate medical education met this summer in Gothenburg, Sweden.

On this occasion I would also like to mention the activities in this field on a national basis of teachers and experts dealing with the problem of medical education in general. Official reports have been prepared by select committees in Europe and in the U.S.A. putting forward particular recommendations regarding preventive and social medicine. Britain has proved particularly active in this respect.

These post-war gatherings, where the duration and the method of teaching social medicine were considered from various angles, finally led to this great Conference, which has been organized in such an admirable manner and on such broad foundations. One of the important features of this Conference is that it is bringing home to the physician generally that medical education is also his business and not only the business of professors and teachers in medical schools.

Before asking our rapporteur to submit his detailed report on our proceedings, I should like to make a few general observations.

No Definition of Social Medicine

We have seen once more, in the course of these last few days, that there exists no definition of preventive and social medicine, and that many authors and lecturers denote the same thing by different names. It would, of course, be good if we succeeded in finding definitions for these ideas which were generally acceptable. Social medicine is sometimes mixed up with definite political programmes. It has, of course, nothing to do with that. It merely endeavours to apply the elements of social science to health problems. With a slight over-simplification it might be termed " the sociology of medicine."

In the course of our proceedings it has been interesting to note how many speakers brought forward the idea that there can be no uniform programmes for the teaching and application of social medicine for use all over the world. The basic line may well be international, but practice and application have to adjust themselves to the geographical features and to the material and cultural development of the various countries.

There seemed to be a general agreement that students should be trained in social medicine in one way or another throughout the duration of their studies, and that particular attention should be paid to the practical work of medical students in institutions, in families, and in field work.

An interesting problem which has come up is the question of the health of the society as such. What should be the criterion and what the standards of measurement? What one authority would consider healthy might be thought unhealthy by another.

Then there is the question of specialization in the various branches of preventive and social medicine—industrial medicine and hygiene, social psychiatry, social paediatrics, and so on. I personally wonder whether that tendency is a good and sound one, especially when we consider that social medicine has still not acquired its due place in many medical schools. It would therefore seem wise, at least for the present, to unite the studies of preventive and social medicine in one department or institute within which the various specialists might concentrate on their respective fields of action.

I have always felt happy when I have seen social medicine achieving progress. I am very grateful to you, ladies and gentlemen, that, owing to your contribution to our proceedings, you have made me experience this particular happiness once more in my life.

Growing Awareness of the Subject

Dr. CHARLES FLETCHER, rapporteur for Section D, spoke as follows:

You will already have gained a glimpse of the benign influence under which we have conducted our affairs with Professor Stampar in the chair. The allocation of a separate Section in this Conference to the discussion of social and preventive medicine, apart from the Section on

the aims and content of the curriculum, is worthy of comment. I take it to reflect a growing awareness of the importance of the subject, but at the same time some perplexity as to its place in undergraduate medical education. This perplexity is manifested by some hostility on the part of those in the more established departments of medicine. There has been in our Section a constantly reiterated claim that in many schools the subject does not receive sufficient attention. Those who advocate the importance of social and preventive medicine do not always define their aims and methods clearly or demonstrate effectively the value of the orientation they seek to give to education in medical science and practice. Only when they have done so will the profession adopt the means by which this orientation can be given.

It is thus appropriate that many of the papers given in our Section have been concerned as much with the meaning of social and preventive medicine as with its teaching. It is my difficult task to attempt to synthesize what has been said, hoping that I may convey its essence with as little distortion as possible. I came to the Conference far from clear in my own mind on this matter; whether I am now clear I must leave you to judge.

Social medicine is a branch of medical science concerned with the study of relations between social and economic conditions and the health of groups of individuals and the individuals themselves, and at the same time an activity concerned with practical measures within the social field that may be taken to promote health, prevent disease, and assist the recovery of the sick. The addition of the term "preventive medicine" brings within the scope of the subject science and practice, technical as well as social measures for the prevention of disease.

The speakers in our Section were all agreed that the good clinician does in his teaching and practice pay attention to social factors in aetiology and in social aids to treatment, but they urged that he can be helped in the elucidation of these social problems presented by his patients by specialists in social and preventive medicine. It is not enough to leave these to medical auxiliaries—the almoner, the health visitor. The social contribution to the medical faculty should be increasingly made by men and women with a full academic and scientific training.

What are the specific subjects which must be covered in this field? First there are the subjects traditionally the concern of classical departments of public health and hygiene—sanitation, epidemiology, control of transmissible diseases, housing, industrial hygiene. The second group of subjects concerns the contribution of the environment—physical, genetic, biological, and social—to the impairment of health, both physical and mental, and the aetiology of disease. These are illustrated in the community by the study of demography and mortality and morbidity statistics, which will show the influence upon disease of occupation, social and economic status, age, climate, and so forth, and it can be pointed out in the course of this discipline that the community consists of individuals upon whom these influences act. They will also show the real health needs of the community that the doctor will serve, and save him from the distorted view of medicine if restricted to hospital practice. One speaker commented on the ignorance sometimes shown by eminent physicians and surgeons as to the real health needs of the community.

The third group of subjects concerns the social structure in which the doctor will work and the various agencies on which he will be able to call to help his patients, a subject of increasing importance now that the State in many countries has swung from an attitude of *laissez faire* to an intense interest in the health and welfare of the individual citizen. The doctor to-day must act as the leader of a team of medical auxiliaries. It is essential that he should understand this team and their functions so that he will use social therapy effectively where this is needed, and not, as is so often done at present, prescribe pharmacopoeial remedies for social needs—the sort of error illustrated by Dr. Dearing, who told of a doctor who gave cod-liver oil and malt to a patient suffering from general undernutrition due to economic causes. Health education also falls into this group.

The Need for Special Departments

Our speakers were unanimous in thinking that special departments are required for the study, practice, and teaching of these aspects of medicine: (1) because of the increasing amount of detailed knowledge and technique that is now accumulating on all these subjects—knowledge which the teacher must fully comprehend if he is to give balanced and accurate and relevant instruction; (2) because special facilities are required for teaching social and environmental influences on health outside the hospital; and (3) because of the opportunities for field research into many of the aetiological factors of disease which still remain obscure. Such research can be most effectively pursued by those who are trained in special departments to use the research methods appropriate to the human populations. Students can often take part in such studies.

Let us now move on to consider some of the detailed methods of instruction that have been suggested in the various aspects of social and preventive medicine. In another Section it has been pointed out that much hospital teaching is irrelevant to the major problems that general practitioners will have to face in the management of their patients, having regard to their circumstances and not just to their diseases. We have had excellent reports of special programmes being organized at various medical schools to bring the student out of the hospital into the surrounding community, and show him under expert guidance how to tackle and think about those problems. The original papers must be consulted for details of such schemes as those at Cornell University, New York, Boston, Edinburgh, Durban, Zagreb, and other centres. There are two types of such schemes. In the first type the student is given a family to follow throughout the whole or part of his medical training. He can thus study both the economic, social, and psychological problems of the family, and also the factors that promote health and cause illness, and judge the effectiveness of the measures he may take as a doctor to influence them. The second type of scheme is one in which members of the faculty of medicine adopt a general practice in which the students play an active therapeutic part, learning the skill required for treatment and aftercare in the home. In some schools in this country the students spend a short period with a general practitioner and play an active part.

Morbid conditions arising from social influences are predominantly psychological and psychosomatic, and in this type of teaching programme it is essential that the psychiatrist should play an important part. These practices will also provide experience for the student in the social agencies available for prevention and therapy. Several speakers emphasized the maturing influence of such practical experience outside the hospital upon the students and also upon the faculty members who guide and supervise their work and to whom they turn for consultation.

Within the hospital various methods of instruction have been suggested. These include the seminar, the conference on given cases between members of the faculty of medicine and specialists in social and preventive medicine.

One interesting form of teaching suggested by one speaker was the collection of tape records of interviews between experienced social workers and patients suffering from organic diseases on which the hospital notes are also available. We were all impressed by the speakers who stressed the importance of this type of field study in relation to child health. It is perhaps in relation to child health that the preventive and curative aspects of social medicine can best be fused and correlated.

In relation to occupational hygiene and industrial medicine there are some who advocate courses of lectures and demonstrations organized by a separate department of industrial medicine. Some instruction in this subject must be given, for the general practitioner must carry the main burden of occupational health. Perhaps the best method of teaching suggested was that it should be given by clinicians on cases

referred from special industrial clinics. A student must be taught to take a full industrial history on every case so that he may appreciate the role of occupation, not only in the impairment of health, but, more important, in rehabilitation and maintenance of health by means of satisfactory and suitable work.

Techniques in Teaching Epidemiology

In our discussions of the content of social and preventive medicine we have been dealing with those subjects which are less immediately concerned with the management of the individual. We have discussed ways and means of making these subjects attractive to the student, already fascinated by clinical problems. One speaker urged that lectures should be given as far as possible by clinicians. The remark of Dr. Mervyn Gordon was recalled, that the teacher of epidemiology should always talk with a stethoscope round his neck. Epidemiology and vital statistics must be taught to a large extent by lectures, and so far as possible should be related to cases that the student sees, though classical illustrations from the past, such as the story of John Snow, must be given to illustrate the triumphs of epidemiological investigation.

Epidemiological techniques, such as Mantoux testing, should, if possible, be carried out by students themselves in appropriate clinics. The use of statistics as a tool for the study of aetiology and to express and illustrate variations from normal must also be related to topics that hold the student's interest. Dr. Pau said that he aroused students' interest in statistics by discussing the subject in relation to bridge, betting on the racecourse, and football pools. The question of normal variation may also be introduced by allowing the student to participate in university student health services. Some teaching of medical genetics is essential, because the doctor will so frequently be asked about this question by mothers who have had abnormal children, or who know they have an abnormal heredity.

The student health service can also be used to introduce the student to his important activities as a health educator, particularly because university students, who will become the future leaders of the community, so often have erroneous ideas on personal hygiene and the preservation of health.

Nutrition is perhaps the most important single environmental influence in the preservation of health, and we had a noteworthy discussion on its teaching. This should permeate all preclinical and clinical studies. Wherever a nutritional disorder is encountered in the clinical years the social and economic causes that led to the condition must be fully examined and discussed. Great emphasis was laid on the necessity of reminding the student of the world-wide problems of undernutrition and the economic and social forces determining the overgrowth of populations and the educative role the doctor may be called on to play in the councils of his country and of the world.

The effects of housing on health can be studied only in the field ; they are best studied, perhaps, through the systems of family supervision already described. In such a field study a student will see the part that bad housing plays in the spread of infectious diseases, the impairment of health, and the production of psychological and psychosomatic disorders.

Subjects such as sanitation which have in the past received much emphasis in the teaching of preventive medicine are now of more concern to engineers rather than doctors. The student should not be burdened with them if more time is to be devoted to the other sectors of social and preventive medicine. Here is one field in which time could be saved.

Our speakers have provided us with no uniform guidance as to the stage in the curriculum at which these subjects should be introduced, but it was felt that the preclinical student should be shown the place of medicine in the community.

A Young Discipline

If what I have said savours of advocacy rather than a dispassionate review of the work of the Section, I have said no more than what I have felt throughout the week. I have had some years of experience in research in industrial medicine, but I cannot claim in any way to be trained in preventive and social medicine any more than any other medical student who went through the clinical training that I received. Social medicine is a relatively young discipline, and has not received the recognition its advocates desire. Its advocates often talk in highly indigestible phrases. Such terms must be repressed if medical men are to listen, and social medicine must base its claim on a clear exposition of effective and comprehensible achievement.

One of the greatest difficulties that a young student must face is a shortage of well-trained and able teachers. This in turn makes it difficult to recruit and train teachers for the future, and so the subject goes by default. The great task that lies before social medicine is to demonstrate with increasing clarity to the medical student that it provides him with opportunities as satisfactory as those provided by organic medicine. We must see to it that the coming generation of doctors pay effective and not only lip service to the fact that prevention is better than cure, and that they show that they have an abiding and active interest in the maintenance of health in the community that they serve.

Sir, we all regret that Professor René Sand, who was to have occupied our chair, has not been with us in person, but I am sure that his spirit has pervaded our deliberations. May I end with two brief quotations from his work. The first: "Social medicine is the final flowering of the preventive and curative art." The other : "The place of medicine is in the stream of life—not on its banks."

Dr. JAMES M. FAULKNER, Dean of Boston University School of Medicine, said that an effort should be made to incorporate into clinical teaching as much of the teaching of social and preventive medicine as possible. In order to obtain effective teaching in this field it was necessary to have university chairs. The ordinary clinical chairs, as the word "clinical" implied, were linked with hospital beds, that is to say, with a controlled environment. If social medicine was to be studied they must go outside the hospital.

Dr. PETER PAU (West Indies) pointed out that social medicine was most highly developed in the countries which needed it least. He hoped that W.H.O. would find means of setting up organizations for social medicine in undeveloped areas.

Dr. A. SPINELLI (University of Rome) spoke of the need for establishing medical education on a world basis, with a curriculum which would be the same for all. He hoped the World Medical Association would utilize the results of this Conference in working out a programme which could be proposed to the Second Conference—"the creation of a physician of the world."

Professor THOMAS FRANCIS (University of Michigan) and Professor VICTOR SORIANO (Uruguay) also briefly addressed the Conference in appreciation of what had been planned and achieved.

The concluding proceedings of the Conference were reported in last week's *Journal* (p. 565).

The British Standards Institution has issued a standard (B.S. 1887 : 1953) for weighing and height-measuring machines used in the Maternity and Child Welfare and School Health Services. It was prepared at the request of the Ministries of Health and Education, the Department of Health for Scotland, and the Scottish Education Department. The standard specifies minimum requirements for the construction, calibration, and accuracy of weighing machines, spring balances for midwives, and height-measuring equipment. Copies may be obtained from the British Standards Institution, Sales Branch, 24, Victoria Street, London, S.W.1. Price 2s. 6d.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Aetiology of Vascular Disease

SIR,—Whilst supporting some of the aetiological views expressed by Professor Charles Wells in his letter "The Egg Maligned" (*Journal*, August 22, p. 443), we do not think that the fat factor in vascular thrombosis can be dismissed so lightly. Dr. H. W. Fullerton and his colleagues (*Journal*, August 1, p. 250) state that alimentary lipaemia increases the coagulability of blood; we would also point out that the serum lipoproteins are increased in both coronary thrombosis and intermittent claudication, and that this rise may fall on giving heparin.

In the matter of tobacco we would endorse what Professor Wells has to say. We have jointly been running a peripheral vascular clinic for some time, and our experience of claudication is, quantitatively at least, greater even than that of Professor Wells. We have taken note of the smoking habits of some 400 patients and so far have met with only two male patients who did not smoke—and one of these was employed in the manufacture of nicotine insecticide. Not only are these patients smokers, but the majority are heavy smokers, as the following figures show: 50 cigarettes or more, 8%; 30–40 cigarettes, 12%; 20–30 cigarettes, 44%; 1–20 cigarettes, 36%.

Those who are strong-minded enough to accept our advice and give up smoking very commonly show a marked and speedy improvement so far as their claudication is concerned, particularly if their consumption of tobacco has previously been very high. Further, several patients who have had superficial phlebitis in association with their arterial disease have not only had relief from this symptom by stopping smoking, but have found that just one cigarette is enough to bring on another attack of phlebitis.

A factor which Professor Wells does not mention is that of vasodilatation by alcohol. Great numbers of our patients with claudication are teetotallers or only have a drink very occasionally: Did not take any, 25%; less than one drink a week, 40%; one or more drinks a week, 35%.

In our general advice to patients with claudication we condemn smoking but allow spirits. We have not yet made up our minds about diet as the exogenous source of the fat which probably plays a part in the pathogeny of the condition.—We are, etc.,

J. B. OLDHAM.
H. S. PEMBERTON.

Liverpool, 1.

Breast-feeding

SIR,—The paper by Drs. Alice Stewart and Celia Westropp on breast-feeding (*Journal*, August 8, p. 305) prompts me to say that the conclusion drawn—namely, that breast-feeding does not diminish the incidence of later illness, is apparently not borne out by my survey of 2,613 children who attended the child welfare centres in Halifax until after they could walk.[1]

Admittedly the criteria are somewhat different. I confined my figures to those for serious illness, because trivial complaints like head-colds are apt to be exaggerated by the mothers in some cases and forgotten in others. Also, I have not recorded the age at which the illness occurred. But the types of illness in the Oxford doctors' Table VII and my Table VI (in which the bottom line has a misprint and should read "All illnesses," instead of "Other illnesses") are roughly comparable, and the Halifax figures show a clear gradient in favour of breast-feeding. This gradient also appears in my later tables, where these illnesses in premature babies, and respiratory illnesses among babies of all birth weights, are considered separately.

I should like, further, to support Professor Illingworth's plea (*Journal*, August 22, p. 441), in his criticism of the Oxford paper, that babies are not necessarily "better because they are bigger." It has been strongly argued on philosophical grounds that the prolongation of infancy characteristic of the human species is a basic factor in the growth of intelligence and of family life. It is therefore at least a possibility that the more rapidly maturing infant presents a pattern of progress biologically less favourable than that of the child developing more slowly. In the light of such a view, any hastened growth due to the stimulus of artificial feeding might be both abnormal and undesirable. The high protein value of cow's milk may be well adapted to the needs of the calf, which takes two months to double its birth weight, but ill suited for the human baby, which takes from five to six months to do the same thing. The suggestion is that artificial foods, which are in principle cow's milk modified more or less, may accelerate unnaturally the physical growth of the human infant.

After a perusal of the Oxford survey, it occurs to me forcibly that all such research would immediately gain by a common agreement amongst those in different centres undertaking this work, not only as to the exact questions to be answered, but also the precise categories to be employed uniformly in classifying the available data—not, of course, to the exclusion of new queries and new categories where these were necessary. This would more readily permit the useful correlation of results from different districts or groups, and might in turn encourage more widespread research into the vital problems of child life and health. Could the proposed new Clinical Research Board further the integration of this research?—I am, etc.,

ELENORA SIMPSON.

Halifax.

REFERENCE

[1] *Med. Offr*, 1953, **89**, 133.

Non-paralytic Poliomyelitis

SIR,—In view of the widespread interest taken in the incidence of paralytic cases of acute anterior poliomyelitis, it is noteworthy that the attention of most observers is directed mainly to this phenomenon of paralysis rather than to what may be termed the true clinical picture of the infectious disease which may give rise to it. It is well known that from 50 to 80% of the adult population possess serum containing protective antibodies against the virus, and this is taken as presumptive evidence of previous infection. If this is true, what is the clinical picture? The mild febrile attacks, transient and trivial, of infancy and early childhood are probably amongst the commonest diseases encountered in general practice, and, owing to their unimportant nature, little real interest is taken in these by parent and doctor alike.

It is with this in mind that I would like to draw attention to one of these mild "chill" syndromes with which all general practitioners must be familiar, and which I have seen many times since the recent increase in cases of poliomyelitis has caused me to view all sick children with an unusually wary eye. The syndrome is as follows: the child, usually under 5 years of age, is quite well and active, playing and eating normally, when it suddenly becomes listless, pale, and rather drowsy—there is no evidence of upper respiratory infection at this stage. Within an hour or two it may vomit, and this may be repeated once or twice. Food is refused, and the temperature, although sometimes remaining normal, may rise rapidly to 102° F. (38.9° C.) or 103° F. (39.4° C.). If old enough to do so, the child may complain of headache. After about eight to twelve hours it looks and feels better, and the temperature drops to normal or nearly so, but there is complaint of sore throat or some difficulty in swallowing. This is transient, lasting only a few hours, and there is no cervical lymphadenitis. Examination of throat at this stage reveals slight injection of pharynx and soft palate, and swabs rarely grow any of the usual organisms expected. As it fades there is rapid recovery. C.N.S. examination reveals normal reflexes and nothing more positive than slight irritability.

In the presence of an epidemic of paralytic cases of poliomyelitis, such a picture is, of course, viewed with suspicion, but similar cases are very common in the absence of such an epidemic,

and are then presumably dismissed as chills, mild pharyngitis, or even attributed to teething. I suggest, therefore, that unrecognized, "abortive" poliomyelitis may be one of the commonest conditions with which we are familiar in our daily practice, but perhaps view with an unseeing eye. If this is true, then so-called outbreaks of poliomyelitis merely indicate a local increase in virulence of the virus, possibly caused by more than usually rapid transference from case to case with the result that invasion and damage of the C.N.S. takes place. In other words, acute anterior poliomyelitis by definition becomes a rare "complication" occurring in an otherwise harmless and widespread disease.

The idea of a sudden increase in virulence resulting in a completely different clinical picture is not a new one, and has been used to explain the increase in severity of symptoms in endemic influenza.—I am, etc.,

Worcester. A. P. GRIMBLY.

Use and Effectiveness of Antimalarial Drugs

SIR,—May I say how interested I was in Dr. B. M. Nicol's article on the use and effectiveness of antimalarial drugs (*Journal*, July 25, p. 177). His results have certainly done much to clarify the position with regard to the various preparations at present being used in West Africa for the suppression of malaria.

Experience in this area of the Gold Coast has largely confirmed his findings. There has undoubtedly been a tendency for expatriates to change from quinine and mepacrine to proguanil and chloroquine, and the most effective doses have been 200 mg. of proguanil daily or 300 mg. of chloroquine twice weekly. In adults I cannot recall having seen malaria in anyone who was on 200 mg. of proguanil daily. There have, however, been numerous instances amongst those taking 100 mg. The only attacks of malaria occurring with chloroquine have been with 300 mg. weekly. With regard to dosage for babies, there is one boy here, now aged 11 months, who is just recovering from his third attack of *P. falciparum* malaria during the last four months. He was taking 50 mg. of proguanil daily, but has been changed to chloroquine 75 mg. twice weekly.

Finally, it may be of interest to note that blood slides taken routinely in Europeans reporting with other complaints frequently show scanty *P. falciparum* rings. These patients often make a complete recovery without receiving any specific antimalarial therapy.—I am, etc.,

Accra, Gold Coast Colony. J. J. MESSENT.

Danger of Penicillin Injection

SIR,—I was very interested to read about the fatal penicillin injection in the medico-legal section (*Journal*, August 22, p. 446). On August 12 I experienced an anaphylactic reaction from penicillin.

On the morning of August 11 I developed a sore throat with a temperature of 99.8° F. (37.7° C.). Next morning I had no temperature and felt well enough to see routine cases. However, my fauces were red and swollen, with slight swelling of the tonsils and considerable pain on deglutition. As I wanted to continue working, 500,000 units of crystalline sodium penicillin and 300,000 units of crystalline procaine penicillin, dissolved in 2 ml. water in one syringe, was given into my left thigh intramuscularly. On withdrawal of the needle a slight spot of blood appeared. Three minutes later my face felt hot, and the surface of the anterior two-thirds of the tongue began to tingle. Then my whole body, particularly limbs, began to itch intensely. Six minutes from the onset I was completely covered by a confluent raised red rash, with a few wheals on my ankles and chin. My face was bloated and unrecognizable, with marked oedema of the lips and cheeks and suffused conjunctivae. I was intensely restless, with a pulse rate of 150 per minute. Within 10 minutes of the onset I was given 1 ml. of 1/1,000 adrenaline intramuscularly, which alleviated the symptoms completely in 30 minutes. Thirteen days later a blood count showed: Hb, 16.4 g.%; white cells, 9,000 (neutrophils 46%, eosinophils 20%, lymphocytes 31%, monocytes 3%). Subsequently the sore throat relapsed and I had 250,000 units of sodium penicillin six-hourly for five days without trouble.

There is no allergic family or personal history. I have received intramuscular injections of sodium and procaine penicillin in the past without reactions. The same batch of penicillin has been used without ill effect, and I have given the combined dose on many occasions.

It seems likely that such a reaction, if untreated, would have progressed to laryngeal oedema in a very short time with fatal results. The danger would appear to be in giving an injection of penicillin and leaving the patient's house within three minutes, which is quite likely in a busy practice. I would like to know whether the two other cases in this country referred to by Dr. J. R. McKenzie were deaths or anaphylactic reactions.—I am, etc.,

Beckenham. E. J. MASTERS.

Medical Education Conference

SIR,—As a general practitioner I derived great satisfaction from the *atmosphere* of the Conference with its insistence on the importance of the training of general practitioners. Eighty per cent. of the population of this country, and up to 95% or more in some parts of the world, are in moderate or poor—sometimes very poor—circumstances. It is mainly from these that the general practitioner draws his patients, and he may truly be said, both literally and metaphorically, to have his finger on the pulse of the nation. The specialist probably does not see more than 10% of the population.

The function of the general practitioner, as I see it, is to keep patients out of hospital unless it is really necessary to send them there. To be efficient he must be fully trained in the use of diagnostic aids, especially the ophthalmoscope and auriscope, and he must be able to write a good letter giving the relevant information when he sends a patient to hospital. Minor surgery is also very important. Few patients with minor surgical complaints need go to hospital, and the student should be taught the techniques which he can safely employ in his own surgery. *He should also be made aware of his limitations.*

It is our duty to posterity to give our successors a better start in life than we ourselves have had. I formed the impression that this has been the primary concern of this very important and interesting Conference. All general practitioners who spoke during the discussions received a courteous and sympathetic hearing, and I had many interesting discussions with professors from many universities from all over the globe. We general practitioners should be grateful to all members of the Conference for the kind interest they have taken in our problems of education.

These are, of course, my own personal views, but I hope they also express those of the other general practitioners there present, and, indeed, of those everywhere.—I am, etc.,

Woodford Green, Essex. ST. GEORGE B. DELISLE GRAY.

POINTS FROM LETTERS

Nasal Drops for Babies

Dr. G. G. JENNER (Dunedin, New Zealand) writes: I was greatly surprised to see chlorbutol and menthol nasal drops (*N.F.*, 1952) recommended for babies' noses by Dr. F. Charlotte Naish (*Journal*, June 27, p. 1442). After all the warnings in the textbooks about the dangers of liquid paraffin in nasal drops causing either damage to the ciliary action of the nasal mucous membrane, or lipoidal pneumonia, and the warnings of instant collapses with menthol in infants' nostrils, I am sure many of us have been frightened off these preparations. Would not a weak solution of ephedrine hydrochloride in normal saline be less harmful? I would be interested to hear an ear, nose, and throat specialist's opinion on this. Possibly the dangers have been much exaggerated, but if they exist at all why not use something perfectly safe if it produces the same result?

Obituary

W. N. SEARLE, M.B., F.R.C.S., F.R.C.O.G.

Mr. W. N. Searle, who was an obstetric surgeon on the staff of the Westminster Hospital, died suddenly on August 30 while at sea. Mr. Searle was on his way to New Zealand.

Walter Netley Searle was born on May 20, 1904, at Oamaru in the South Island of New Zealand. From Waitaki Boys High School he went on to study medicine at the University of Otago Medical School, Dunedin, where he graduated M.B., Ch.B. in 1929. Shortly afterwards he came to Britain as a postgraduate student, and was appointed resident obstetric officer at the Royal Maternity and Women's Hospital, Glasgow. In 1931 he was elected F.R.C.S.Ed. He then moved to London, where his first posts were those of house-surgeon and resident medical officer at the Chelsea Hospital for Women. His work soon won notice, and after holding an appointment as registrar and radium officer at the Chelsea Hospital for Women he became gynaecological registrar and tutor at the Westminster Hospital. In due course he was elected to the honorary staff of both these hospitals. He became F.R.C.S.(England) in 1937 and F.R.C.O.G. in 1948. Among the subsidiary appointments which he held were those of obstetric consultant to the Borough of Enfield and gynaecological surgeon to the East Ham Memorial Hospital, and he examined for the Central Midwives Board, the Royal College of Obstetricians and Gynaecologists, and the Society of Apothecaries.

Mr. Searle was a most able gynaecological surgeon, and the quality of his work and charm of manner quickly won him success in London. He married Cissie, daughter of Professor R. Bell, of Otago University, and her devoted and unselfish loyalty during her husband's long illness won the admiration of all their friends, who will wish to express to her and to her son their profound sympathy.

Dr. H. LL. RUTTER, who died on June 16 at the age of 85, was one of those who served on the Insurance Acts Committee of the British Medical Association in the early days of its work. Hubert Llewellyn Rutter was born at Mere, Wiltshire, on September 20, 1867, and was one of the younger members of a large Quaker family. Having decided on medicine as a career, he studied at the London Hospital, and qualified M.R.C.S., L.R.C.P. in 1891. He took the degrees of M.B., B.S. at Durham University in the following year, and obtained the diploma of F.R.C.S. in 1894. Two years later he proceeded to the M.D. and took the Cambridge D.P.H. At the London Hospital he held the appointments of house-surgeon and house-physician, and, at the suggestion of Sir Frederick Treves, he then spent some time with the late Sir Wilfred Grenfell in his Mission to Deep Sea Fishermen. In 1900 Dr. Rutter settled in private practice at Newcastle-upon-Tyne, where he became one of the leading local practitioners. He was a member of the Insurance Acts Committee from 1917 to 1920, when he was appointed a whole-time regional medical officer of the Ministry of Health for the north-east division. In 1925 he was transferred to Birmingham, where the remainder of his life was spent. When he retired from the post of regional medical officer in 1932 he returned to private practice. During the two world wars he was closely associated with the work of the Friends Ambulance Unit. In the first war he acted as liaison officer between the unit and Army authorities, for which service he was appointed M.B.E. in 1918. In the last war he gave his time and energies almost entirely to training successive teams of F.A.U. members, teams which went to every country affected by the war. In later years he regularly attended the short postgraduate courses given at the London Hospital, his last visit being in 1952, about the time he retired from practice. He fell ill almost immediately afterwards, and died after many months of suffering. The characteristics which impressed all who knew Dr. Rutter were his indomitable energy, his alertness, and the enthusiasm with which he carried out all that he undertook. He had been brought up in a deeply religious home, and throughout his life he gave himself equally to his medical practice and his religious and social work for the Society of Friends and the Adult School Movement. He felt always that physical health was largely dependent on social and spiritual well-being: he gave himself wholeheartedly to the development of each.—W. H. D.

Mr. PHILIP TALBOT died suddenly at his home, Coed-y-Castell, Deganwy, North Wales, on July 28, aged 73 years. Born in Rochdale, Lancashire, he was the eldest of three brothers, all of whom entered the medical profession. He had a brilliant career as a student at Owens College, Manchester, where he was awarded the junior and senior Platt Exhibitions in physiology and medals for practical anatomy, pathology, morbid anatomy, gynaecology, and medicine. He passed the primary examination for the F.R.C.S. diploma at the time of taking the second M.B. Having graduated in 1904, he was elected to the Tom Jones surgical research scholarship. Two years later he obtained the F.R.C.S. After two years as house-surgeon at the Manchester Royal Infirmary and the District Infirmary, Ashton-under-Lyne, he joined the late Dr. Thomas Clifford in practice in Stalybridge, Cheshire. In 1909 he was appointed assistant honorary surgeon to the District Infirmary, Ashton-under-Lyne, and in 1915 received senior honorary status there, a position he filled with distinction up to his retirement. During the first world war he converted his home into a military hospital and treated many of the early Allied casualties there. He then served as captain at the 23rd British Stationary Hospital, Bagdad, from 1916 to 1918 and was mentioned in dispatches for the excellent work he performed there. Soon after his return home he published a paper on the successful treatment of 15 cases of liver abscess by aspiration. On returning to practice again, he acted as referee to the Ministry of Pensions and medical arbitrator to the courts of law. He retired from active work in 1938 to his beautiful new home in North Wales. He is survived by his widow and one daughter.

A. W. writes: I was privileged to work with Mr. Talbot as his junior partner for four very happy years prior to his retirement. A strikingly handsome man of magnificent physique with the kindest and most gentle of manners, he inspired a wonderful confidence in all our patients—a confidence fully justified by his vast clinical knowledge and experience. I profited enormously from this huge storehouse—dispensed with a humour, charm, and originality peculiar to himself. A first-class sportsman, with a strong love of the moors, rivers, and sea, he obtained great enjoyment from his favourite hobbies of shooting, fishing, and yachting. As a pioneer motorist he was one of the first to appreciate the value of a car in his work. He felt the loss of his two young sons very keenly, the elder dying during his war service and the younger shortly after Mr. Talbot's retirement. A leader of men wherever he went, we can temper our sorrow with the wonderful memories he has left behind him.

By the death of Dr. K. E. ECKENSTEIN on August 23 the French Hospital and Dispensary in London has lost an old and valued member of its medical staff. Kenneth Edward Eckenstein was born in Alsace on July 8, 1881. He studied medicine in this country at St. Thomas's Hospital, qualifying in 1906 and graduating M.B., B.S. in the following year. After holding a number of appointments in hospitals in London, including the Victoria Hospital for Children, the Great Ormond Street Children's Hospital, and the

Chelsea Hospital for Women, he went to Bordeaux to work as an assistant in the clinical laboratory there. In the years which followed he published several papers on the diagnosis of syphilis and on other serological and pathological subjects. He returned to practice in London, and for many years was honorary pathologist to the French Hospital, where shortly after qualification he had held the posts of junior and senior resident medical officer. For a time he was also assistant pathologist to the National Hospital for Diseases of the Heart. During the first world war he served as a civil surgeon in France, and was later commissioned as an officer in the French Army Medical Service. For his work during the war he received a number of decorations, including the Order of the Crown of Belgium, the Croix de Guerre, and the Legion of Honour. After the war he continued his association with the French Hospital and was for some years physician to out-patients there. At the time of his death he was consultant physician to the hospital. He was well known to the French community in London, and was medical officer to the French Consulate. A popular member of the Chelsea Clinical Society for over 40 years, Dr. Eckenstein held office first as honorary secretary from 1911–14, and then as honorary treasurer from 1914 to the time of his death. He was also president of the Society in 1928–9. He leaves a wife and one daughter.

G. E. P. writes: The news of the death of Kenneth Eckenstein will be indeed sad for his innumerable friends, both in England and beyond these shores. He had a mind which possessed all those qualities of learning and erudition which are so rare in this day and age. Those who were privileged to call him friend will long remember the hours spent with him listening enthralled to the wonderful word pictures which he would paint—pictures of bygone civilizations and of life as it was around the coast of the Mediterranean a thousand years ago. One felt he had been there and knew it all, and that we had been transported in reality to see the colour, light, and shade of those so different ages. When he spoke, and in whatever discussion, on public or private occasion, Eckenstein brought a lively and mordant wit, a broad humanity, and a knowledge of eternal verities which is given to few, and his bluff geniality will long be missed by the members of the Chelsea Clinical Society of London whose treasurer he was for many years. An Alsatian by birth, he spoke perfect English, French, and German, and the wide circle of his contacts gave him a depth of understanding of men and women of many nations and conditions, and this understanding he shared freely with all who knew and loved him. We share with his many friends, both English and of the French colony in London, a great loss and a great sorrow, and send our deepest sympathy to his wife and daughter.

Universities and Colleges

UNIVERSITY OF ABERDEEN

At a Graduation Ceremony on July 9 the degree of D.Sc. was conferred on A. H. H. Fraser, M.D.

FACULTY OF ANAESTHETISTS
ROYAL COLLEGE OF SURGEONS OF ENGLAND

The following courses have been arranged to take place at the College this autumn:

A two-weeks course of sixteen lectures in pharmacology will be held from October 19 to 31. (Fee, £6 6s., or 10s. each for single lectures.)

A three-weeks course of forty lectures in anaesthetics, plus clinical work in medicine and tutorials, will be held from October 12 to 30. (Fee, £34 13s. for the full course, £15 15s. each for lectures and tutorials, £3 3s. for clinical conferences, or 10s. per lecture.) Similar courses will be arranged in the spring of 1954. Further details and application forms may be obtained from Mr. W. F. Davis, Secretary, Faculty of Anaesthetists, Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.2.

Vital Statistics

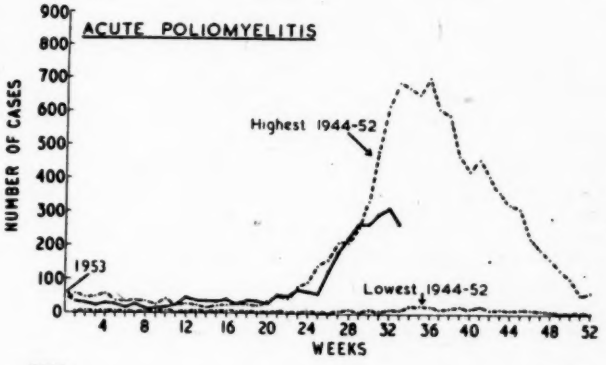
Poliomyelitis

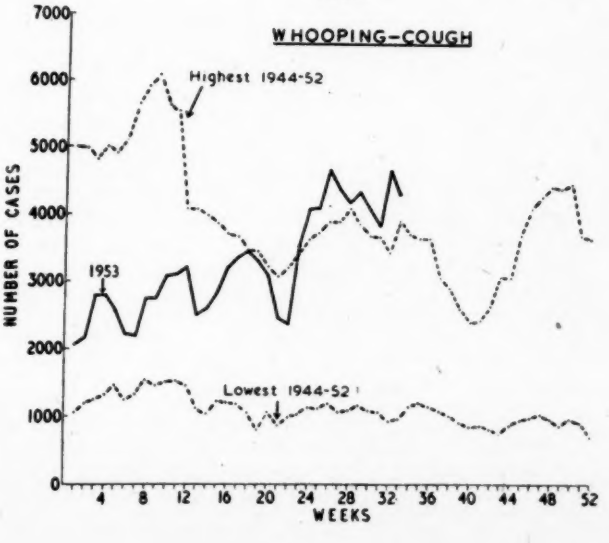
Poliomyelitis notifications (uncorrected) in the week ended August 29 (34th week of the year) were as follows: paralytic, 120 (144); non-paralytic, 117 (126); total, 237 (270). This is a decrease of 33 compared with the previous week, the figures for which are in parentheses. The individual districts which have notified 20 or more cases in the year to August 29, with incidences per 100,000 in parentheses, are as follows: Southend-on-Sea C.B., 46 (30.36); Liverpool C.B., 51 (6.44); Birmingham C.B., 61 (5.45); Coventry C.B., 114 (43.68); Leicester C.B., 28 (9.79); Lewisham M.B., 25 (11.01); Blackpool C.B., 29 (19.69); Camberwell M.B., 22 (12.14); Islington M.B., 24 (10.20); Bournemouth C.B., 36 (25.91); Bristol C.B., 26 (5.86); Nottingham C.B., 24 (7.72); Taunton M.B., 26 (75.14); St. Pancras M.B., 23 (16.48); Carlisle C.B., 25 (36.82); Manchester C.B., 22 (3.12); Wandsworth M.B., 20 (6.63); Southampton C.B., 20 (11.40); Atherstone R.D., 20 (84.39); Leeds C.B., 21 (4.16).

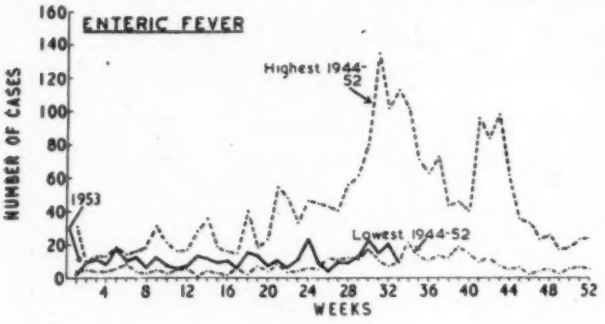
Notifications in the 34th week continued to drop, and there were 24 paralytic and 9 non-paralytic fewer than in the preceding week. This is satisfactory, and cautious optimism is justified.

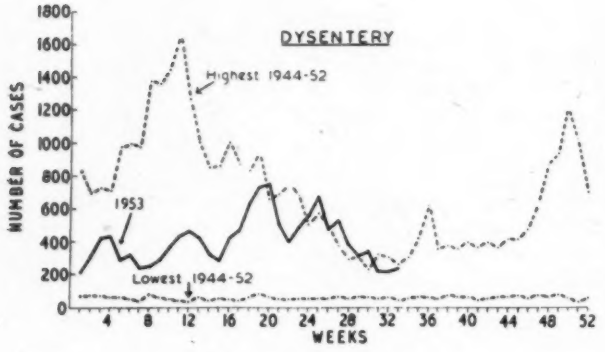
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1944–52 are shown thus - - - - - - -, the figures for 1953 thus ————. Except for the curves showing notifications in 1953, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

There was a general decline in the incidence of infectious diseases in England and Wales during the week ending August 22. The falls in the number of notifications included 565 for measles, from 2,123 to 1,558; 340 for whooping-cough, from 4,681 to 4,341; 57 for scarlet fever, from 488 to 431. The only exception to the declining incidence was a rise of 18 for dysentery, from 217 to 235.

The largest fall in the incidence of measles was 97 in Lancashire, from 312 to 215. The number of notifications of scarlet fever was the lowest for recent years and was 5 below the low level of 1947; only small variations occurred in the local trends during the week. The largest declines in the local incidence of whooping-cough were 61 in Yorkshire East Riding, from 126 to 65; 67 in Middlesex, from 226 to 159; and 59 in Kent, from 263 to 204. 11 cases of diphtheria were notified during the week, being 11 fewer than in the preceding week. The chief feature of the returns of diphtheria was a fall in Lancashire from 8 to 2.

270 cases of acute poliomyelitis were notified, being 42 fewer for paralytic and 6 fewer for non-paralytic cases than in the preceding week. The largest returns were Warwickshire 32 (Coventry C.B. 11, Birmingham C.B. 5, Atherstone R.D. 5, Royal Leamington Spa M.B. 4), Lancashire 21 (Liverpool C.B. 6, Rochdale C.B. 3), Essex 20 (Wanstead and Woodford M.B. 5), Kent 16, Yorkshire West Riding 15, London 14, Dorsetshire 13 (Poole M.B. 6), Cumberland 11 (Carlisle C.B. 8), Surrey 10, and Southampton County 10.

The largest returns of dysentery were Lancashire 31 (Liverpool C.B. 12), London 28, Kent 23, Yorkshire West Riding 16, Cheshire 15 (Marple U.D. 9), Middlesex 12, and Warwickshire 12 (Birmingham C.B. 12).

A further 53 cases of food-poisoning were notified from the outbreak in Flintshire, Prestatyn U.D., where 59 cases were notified in the preceding week.

Week Ending August 29

The notifications of infectious diseases in England and Wales during the week included scarlet fever 443, whooping-cough 4,170, diphtheria 16, measles 1,049, dysentery 206, paratyphoid fever 16, typhoid fever 1, and food-poisoning 194.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **August 22** (No. 33) and corresponding week 1952.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1953					1952				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	11	0	4	0		17	2	6	0	3
Dysentery	235	28	68	5	2	125	31	93	4	2
Encephalitis, acute	5	0		0		11	4	1	0	
Enteric fever:										
Typhoid	3	1	1	0		4	1	0	0	3
Paratyphoid	7	0	0	0		40	2	2	0	1 (B)
Food-poisoning	339	12		0		146	15		1	
Infective enteritis or diarrhoea under 2 years				30	33				22	20
Measles*	1,558	29	24	23	40	6,099	751	37	55	81
Meningococcal infection	14	1	10	4		35	1	7	0	3
Ophthalmia neonatorum	32	3	7	0		34	1	8	0	
Pneumonia†	194	14	78	5	1	247	11	136	5	
Poliomyelitis, acute:										
Paralytic	144	9	11	24	8	170	16	8	7	4
Non-paralytic	126	5				88	6			
Puerperal fever§	247	43	10	0	2	242	30	12	3	
Scarlet fever	431	27	99	16	21	643	55	137	11	47
Tuberculosis:										
Respiratory			137	20				101	30	
Non-respiratory			25	4				19	6	
Whooping-cough	4,341	394	356	40	52	1,872	100	66	50	151

DEATHS in Great Towns	1953					1952				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0		0	0
Dysentery	1	1	1	0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0		0	
Infective enteritis or diarrhoea under 2 years	6	1	2	2	0	3	0	2	2	0
Influenza	3	1	0	0	0	6	0		0	0
Measles		0	0	0	0		0		0	0
Meningococcal infection		0	0				0			
Pneumonia	100	9		8	1	113	14		4	7
Poliomyelitis, acute	8	2			0	8	1			
Scarlet fever		0	0	0	1		0		0	0
Tuberculosis:										
Respiratory	65	3	13	3	3	85	10	13	1	5
Non-respiratory		2	3	0	0		1	3	0	0
Whooping-cough	2	0	2	0	0	1	0		0	0
Deaths 0–1 year	180	26	27	7	3	185	20	25	4	8
Deaths (excluding stillbirths)	3,891	578	481	92	116	4,030	567	501	90	107
LIVE BIRTHS	7,592	1156	820	226	449	7,683	1174	838	215	444
STILLBIRTHS	162	22	16			191	22	21		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Charles Darwin's House.—The custody of the national memorial to Charles Darwin at Down House, Kent, has been transferred to the Royal College of Surgeons by the British Association. Darwin lived at Down House for 40 years, from 1842 to his death in 1882, and it was there that he wrote *The Origin of Species*. In 1927 an opportunity arose of acquiring the property for the nation, and Sir Arthur Keith, then president of the British Association, made a public appeal which was immediately answered by Sir Buckston Browne, F.R.C.S. He bought the property and restored it; and with the help of members of the Darwin family and others he collected for display in the public rooms many priceless relics connected with Darwin. The property and its contents were presented to the British Association, and the memorial was opened to the public in 1929. Since then it has been visited by thousands of people every year except during the war.

Medical Research Council.—Professor Robert Platt, professor of medicine at Manchester University, and Professor E. C. T. Spooner, professor of bacteriology and immunology at the London School of Hygiene and Tropical Medicine, have been appointed members of the Medical Research Council. Their term of office is from October 1, 1953, for four years.

World Federation for Mental Health.—"Social Provision for Mental Health" was the theme of the sixth annual meeting of the World Federation for Mental Health which was held at the University of Vienna from August 16 to 22. Dr. H. C. Rumke (Holland) was elected president. At the first plenary session Dr. J. R. Rees, medical director of the World Federation, addressed the conference on recent trends in mental health. He described some of the factors tending to the development of the well-integrated personality. Other subjects discussed at the Conference, which was attended by nearly 400 members and delegates from 26 countries, were: "Aid in Mental Sickness"—a three-day symposium which dealt with the contributions of the community and the family and with the effects of community provision on family life; the relationship of various factors, such as alcoholism, juvenile delinquency, and social security, to mental health; and the rehabilitation of handicapped children. At the annual meeting of the European League for Mental Health, which took place during the Conference, Dr. Doris Odlum was inaugurated as president of the League for the next three years. It was announced by Dr. Rees that the third Triennial Congress of the World Federation for Mental Health will be held next year in Toronto (August 14–21).

Clinical Meeting in the Canal Zone.—During the recent visit to the Canal Zone of Sir Stanford Cade, civil consultant in surgery to the Royal Air Force and honorary consultant in radiotherapy to the Army, and of Air Commodore F. W. P. Dixon, consultant in surgery to the Royal Air Force, a clinical meeting was held on August 28 at the British Military Hospital at Fayid. Major-General W. A. D. Drummond was in the chair and 160 medical officers from the three Services attended. After the presentation of cases a demonstration was given of a method of mass inoculation (originally described by Sir Alexander Fleming) which has recently been introduced into the Canal Zone. Sir Stanford Cade then addressed the meeting on the progress of medical science during the last 30 years in the treatment of malignant disease. The main session of this successful meeting was attended by the Commander-in-Chief, General Sir Cameron Nicholson, and officers of his staff.

APPOINTMENTS

GILLORAN, JAMES L., M.B., Ch.B., D.P.H., Senior Deputy Medical Officer of Health for the City of Edinburgh.

SMYTH, DESMOND ALCORN, M.B., B.S., D.P.H., Medical Officer of Health, Bilston Municipal Borough.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Treatment of Subacute Combined Degeneration of the Cord

Q.—*What is the best treatment for subacute combined degeneration of the cord? Is there any known association between this disease and pulmonary tuberculosis? I have a patient with both conditions.*

A.—The essence of treatment in subacute combined degeneration of the cord is the parenteral administration of vitamin B_{12} in adequate dosage. The interpretation to be put upon the word "adequate" varies with the stage of the disease. When the diagnosis has only recently been established and the blood level has not been restored to normal, 100 μg. once a week is a reasonable dose; this should be continued until the red blood cell count exceeds 4,500,000 per c.mm., the haemoglobin level has reached 95% (Haldane), and the mean corpuscular volume has fallen below 100 μ^3. For the next year, 50 μg. weekly is sufficient. By the end of that time it is likely that the nervous symptoms will have improved as much as can be expected, and then 100 μg. once a month will be an adequate maintenance dose. There is no reason for believing that liver extract or any other preparation is required in addition to vitamin B_{12}. A full diet with a supplement of vitamins is a logical adjuvant, and recovery is helped by physiotherapy.

There is no known relation between pulmonary tuberculosis and subacute combined degeneration of the cord. In one series of patients with pernicious anaemia only 0.27% had pulmonary tuberculosis.[1] Tuberculous stricture of the intestine and tuberculous mesenteric lymphadenitis may be associated with a megaloblastic anaemia, but accompanying neural degeneration is of extreme rarity.

REFERENCE

[1] Wilkinson, J. F. (1933). *Quart. J. Med.*, n.s., **2**, 281.

The Sexual Hair

Q.—*What is the origin and function of pubic and axillary hair?*

A.—This is an interesting question. If by "origin" is meant, "What is the hormone mechanism responsible for sexual hair?" then the answer is androgens secreted by the adrenal gland; in the case of the male, the androgens secreted by interstitial cells of the testis also contribute. It was formerly thought that in the female pubic and axillary hair was produced by oestrogens, but this is not true, or at any rate it is not true that oestrogens give a direct stimulus. If oestrogens are given to a case of panhypopituitarism no sexual hair results, because the mechanism of the oestrogen action in regard to sexual hair is to stimulate adrenal androgenic function via the pituitary A.C.T.H. secretion. If oestrogens are given to a patient whose pituitary is intact, androgens from the adrenals then produce sexual hair. If androgens—for example, testosterone—are given directly, pubic and axillary hair will result whether the pituitary gland is present or whether it is destroyed, as the action of the androgens is directly on the hair follicles of the skin.

As to the second part of the question, the function of sexual hair, this is a matter on which I can write with less expert knowledge. It is generally assumed that sexual hair helps to absorb or take up perspiration, and is therefore present where perspiration is more evident. This would apply more to axillary hair than pubic hair. The pubic hair might also be regarded as being protective to a sensitive

part of the body and perhaps even making that part of the body less obvious than it might be, but this is conjectural. The eyebrows, which also might come into a similar category, are regarded as protecting the eyes both from excessive light and from the perspiration of the forehead.

Should an Epileptic ever Drive a Car?

Q.—*Should the ban on an epileptic driving a motor vehicle be absolute and lifelong, or can the rule safely be relaxed sometimes? For instance, might an epileptic whose fits have been effectively controlled for several years by drugs be allowed to drive, or one whose fits occurred only at night or a sufferer from petit mal? If some relaxation is permissible, please say what criteria must be satisfied to qualify an epileptic for a driving licence.*

A.—The applicant for a driving licence is required to answer yes or no to the question, "Do you suffer from epilepsy?" He is instructed if in doubt to get professional advice. There is no provision in law which defines the time which must elapse from the occurrence of a seizure before the applicant for a driving licence may be certified as not liable to fits, but when the regulations for a driving licence were drawn up the Ministry of Transport was advised by a committee appointed by the British Medical Association that the only condition for practical purposes which should be constituted an absolute bar to the issue of a driving licence was epilepsy; however, no legal ruling on this was made.

The doctor cannot advise anyone who has had an epileptic seizure at any time to answer no to the question contained in the application form. If, however, he believes in a particular case that it would be reasonable for an application to be considered from a person who has at one time had seizures, he can give the applicant a statement to this effect, with a note of the time (to the best of his belief) which has elapsed since the last attack, and the date on which treatment ceased. This statement the applicant can then present to the local authority. It must be clearly realized, however, that minor seizures are as dangerous in a driver as major attacks.

Cyclical Buccal Ulceration

Q.—*For seven days before the onset of each menstrual period a woman of 21 suffers from large ulcers of the gums and buccal mucous membranes. These heal completely at the onset of the period. Bacteriological examination of the ulcers has proved negative, and pelvic examination has at all times been normal. She has been treated with local applications to the ulcers and with oestrogens, but without success. What treatment is advised?*

A.—Cyclical buccal ulceration occurring in relation to menstruation is a well-recognized condition, and there is often, but not always, coincident ulceration of the vulva, lower vagina, or anus. It has been the subject of several questions during recent years, and replies were published in the *Journal* (June 15, 1946, p. 940; March 15, 1947, p. 365; and August 21, 1948, p. 408). The situation has not changed materially since then; the cause of the condition is unknown and its treatment is empirical and unsatisfactory. Some relationship to hormonal levels is suggested by the association of ulceration with menstruation and by its almost invariable disappearance during pregnancy. An allergic basis is suggested by the fact that the lesions resemble herpes and because there is often a familial history of other allergic conditions.

Before deciding about treatment general diseases, especially deficiency states, including anaemia, should be excluded; also oral sepsis. It may also be worth while arranging for skin sensitivity tests. Unless these investigations give any lead, treatment has to be empirical. Antihistamine preparations of one sort or another should be tried first, and, if these fail, progesterone or chorionic gonadotrophin. Large doses of vitamin C and sodium hyposulphite 10 gr. (0.65 g.) three times a day appear to help in some cases.

Filatov's Tissue Therapy

Q.—*What is known about Filatov's tissue therapy? Is it any good?*

A.—Filatov's tissue therapy is based on the principle that if animal tissues after death are exposed to conditions unfavourable for their existence "biogenic stimulants" develop which bestow on the tissues the capacity to "stimulate" living cells. Refrigerated skin and placenta are said to be especially effective. There is no rational foundation for this theory, and, apart from a few references by Russians in the French literature, all work on the subject is in Russian journals, and it is not a technique that has been studied elsewhere.

Resuscitation After Coal-gas Poisoning

Q.—*Is there any agreed time limit for the carrying on of artificial respiration with CO_2 and oxygen to resuscitate the apparently dead person who has used coal-gas with suicidal intent? I am assuming that the body is still warm and there is no rigor mortis.*

A.—No, it is quite impossible to fix such a limit. Unlike electrocution, by the time the person is apparently dead the saturation figure of the haemoglobin with carbon monoxide is inevitably high and the process is not merely one of resuscitation but also of getting rid of the carbon monoxide. If there is no sign of life at the end of 20 minutes it can be safely said that the person is dead.

N.F. Lotions for Acne

Q.—*Please tell me which lotions in the "National Formulary" are intended for the standard treatment of acne? Are lot. sulphur. co. and lot. potass. sulphurat. c. zinc. suitable? If so, when should each be used?*

A.—Both lotions are suitable, controlling infection and provoking a reaction with desquamation which helps to remove blackheads. Lot. sulphur. co. is a milder application, suitable for less severe cases. Where the skin is coarse and blackheads are profuse lot. potass. sulphurat. c. zinc. is more valuable.

Muscle Extracts

Q.—*What are muscle extracts? Have they any beneficial effect in angina pectoris?*

A.—The most familiar muscle extract on the market before the last world war was "lacarnol." This was prepared from heart muscle and believed to contain some humoral agent which caused vasodilatation, and it was therefore used by some for any angiospastic state. Therapeutic trials, however, were not encouraging. In any muscle extract the presence of small quantities of histamine has to be considered. At the present time, so far as the writer knows, there is on the market no muscle extract of proved potency as a vasodilator.

NOTES AND COMMENTS

Correction.—The Royal Institute of Public Health and Hygiene points out that, contrary to what was stated in the Educational Number of August 29 (p. 505), there is no longer a Part I course for the Conjoint Board examination for the Diploma in Industrial Health. All candidates for that subject are first required by the regulations of the Board to be in possession of a recognized C.P.H.

All communications with regard to editorial business should be addressed to The EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 4499. TELEGRAMS: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.
Authors desiring REPRINTS should communicate with the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1, on receipt of proofs.
ADVERTISEMENTS should be addressed to the Advertisement Manager, B.M.A. House, Tavistock Square, London, W.C.1 (hours 9 a.m. to 5 p.m.). TELEPHONE: EUSTON 4499. TELEGRAMS: *Britmedads, Westcent, London.*
MEMBERS' SUBSCRIPTIONS should be sent to the SECRETARY of the Association. TELEPHONE: EUSTON 4499. TELEGRAMS: *Medisecra, Westcent, London.*
B.M.A. SCOTTISH OFFICE: 7, Drumsheugh Gardens, Edinburgh.